The American Journal of Medicine

July 1948

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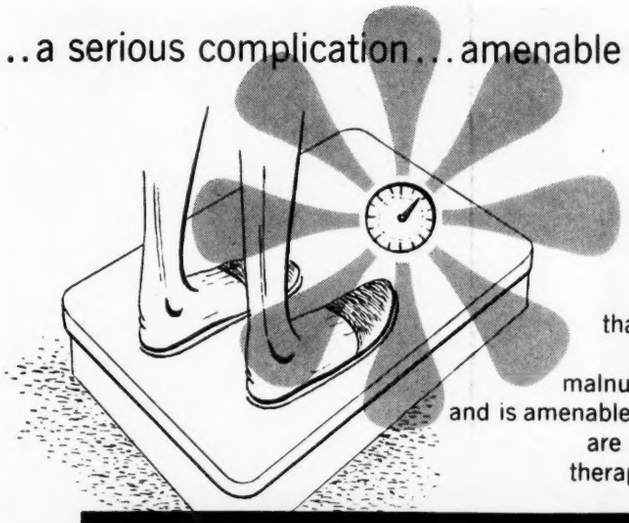

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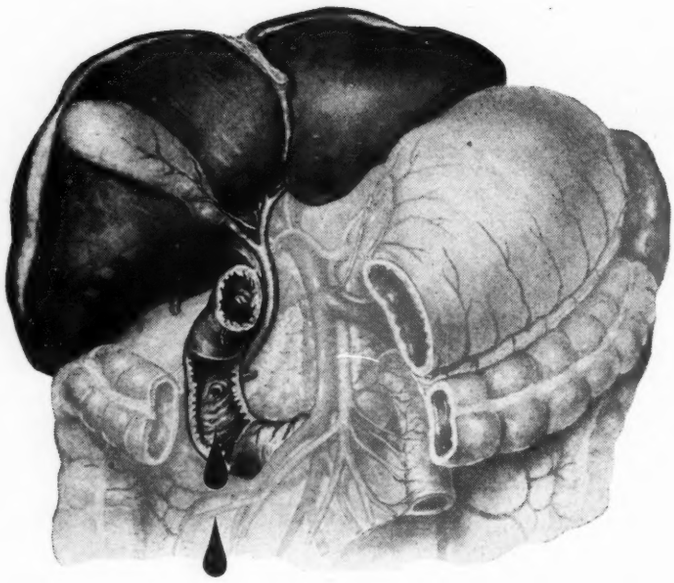

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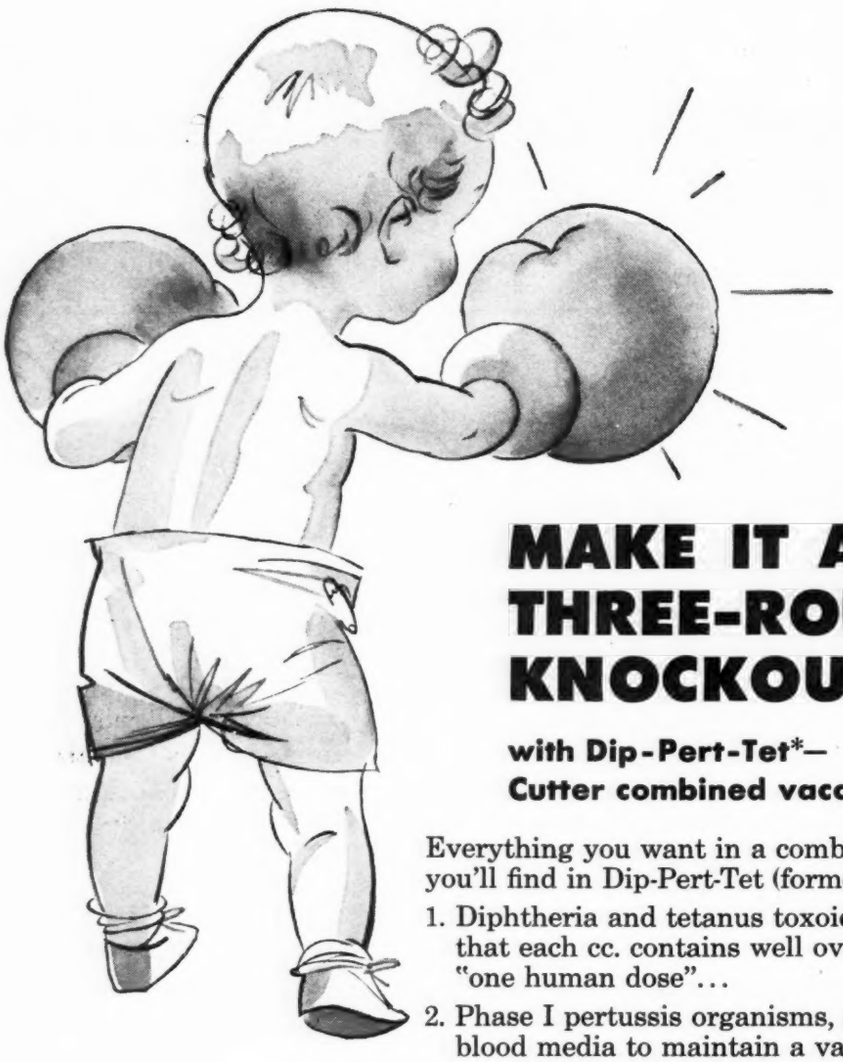

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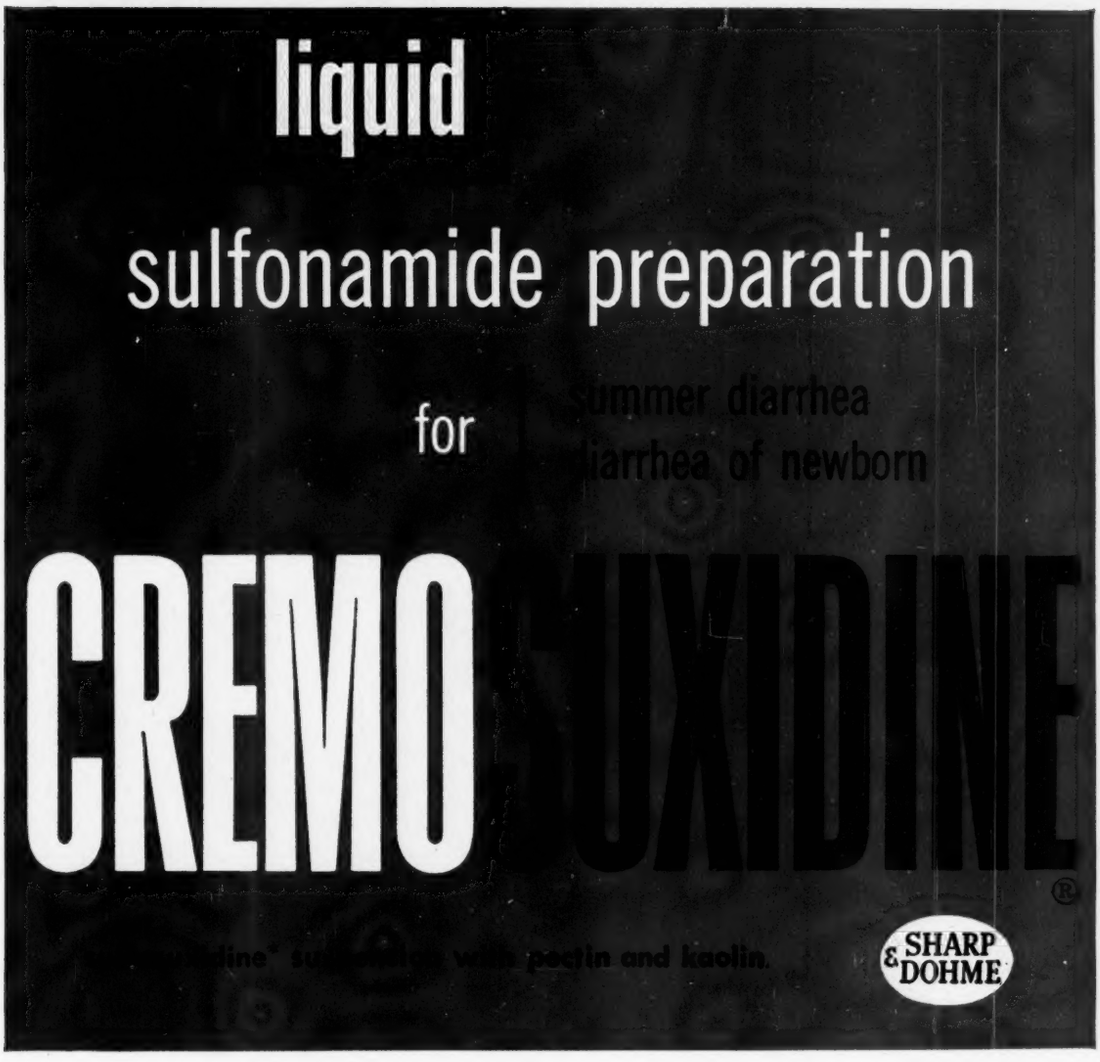

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1. Frant, S., and Abrahamson, H.: *Brennemann's Practice of Pediatrics*, *1*:28:22, 1945.
2. Blattner, R. J.: *J. Pediatrics*, *32*:220, February, 1948.

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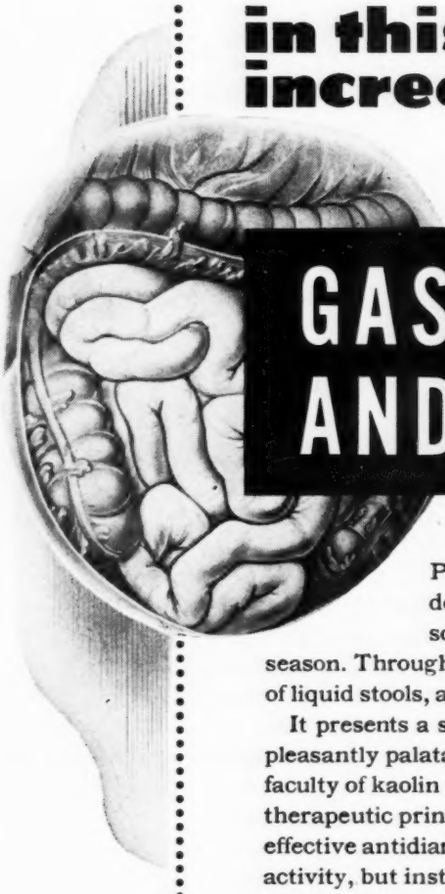

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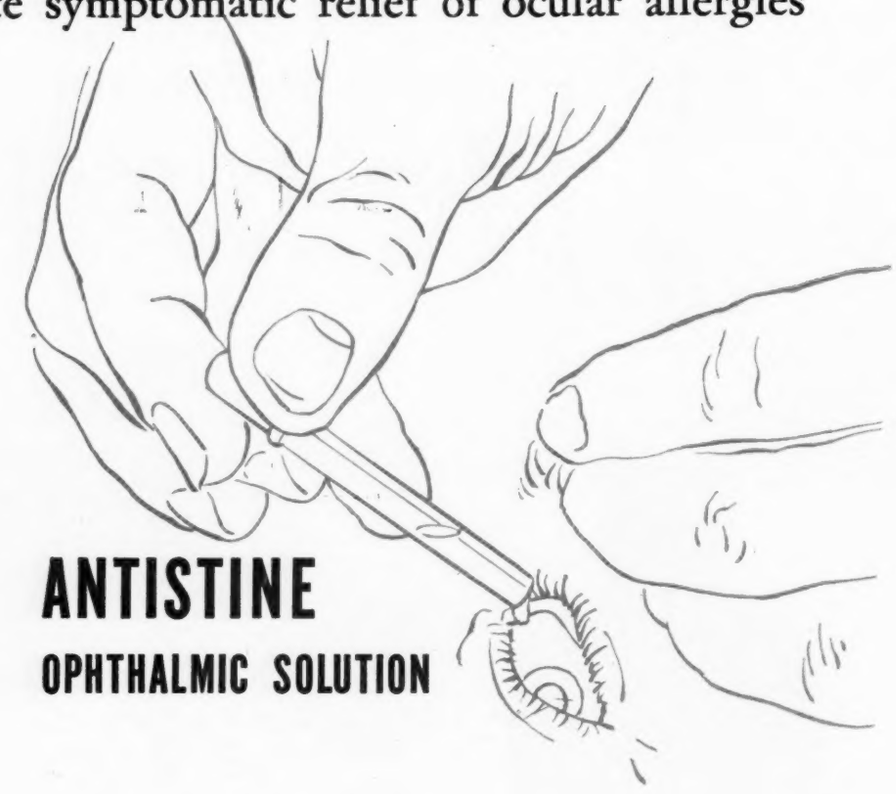

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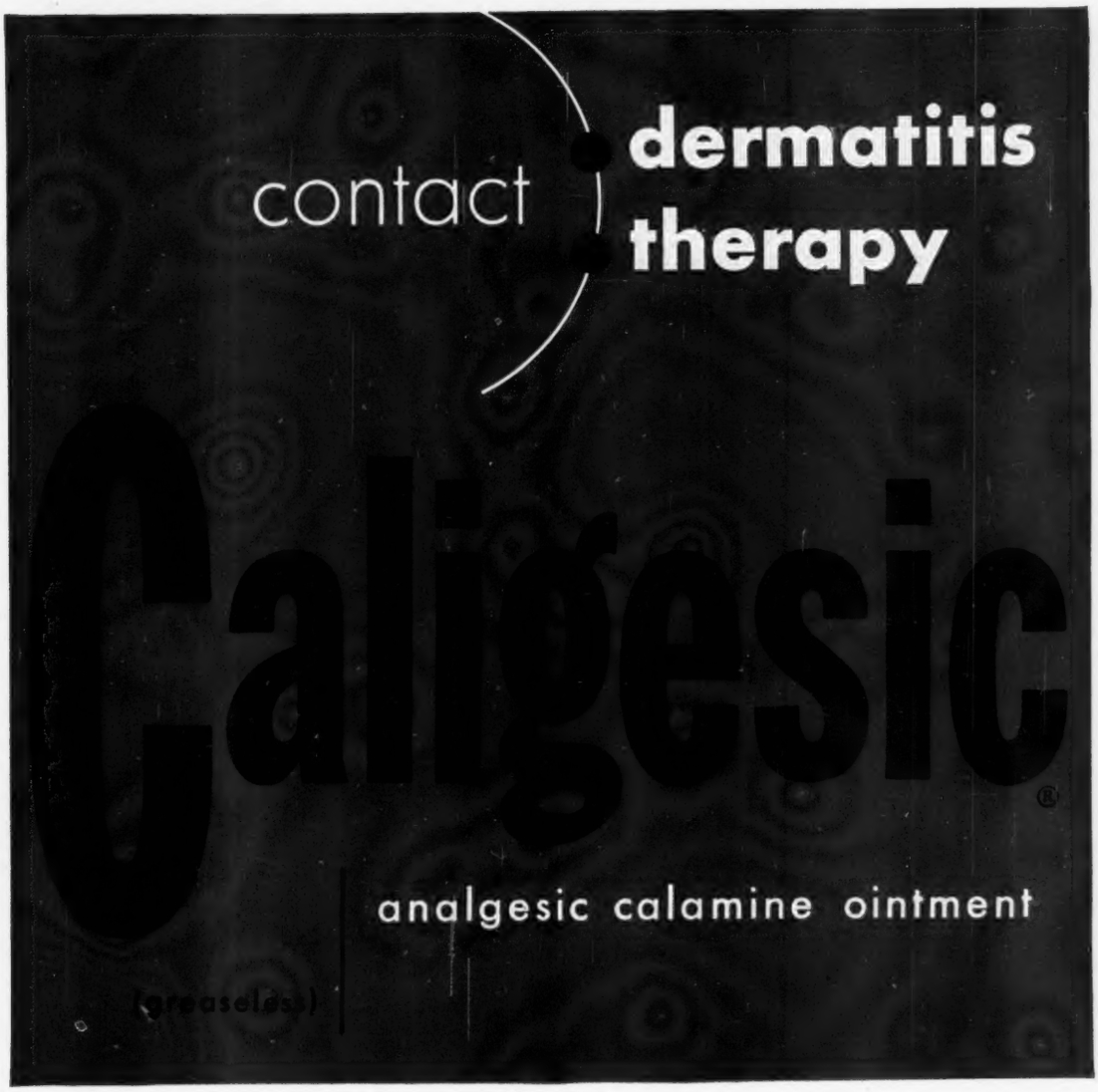

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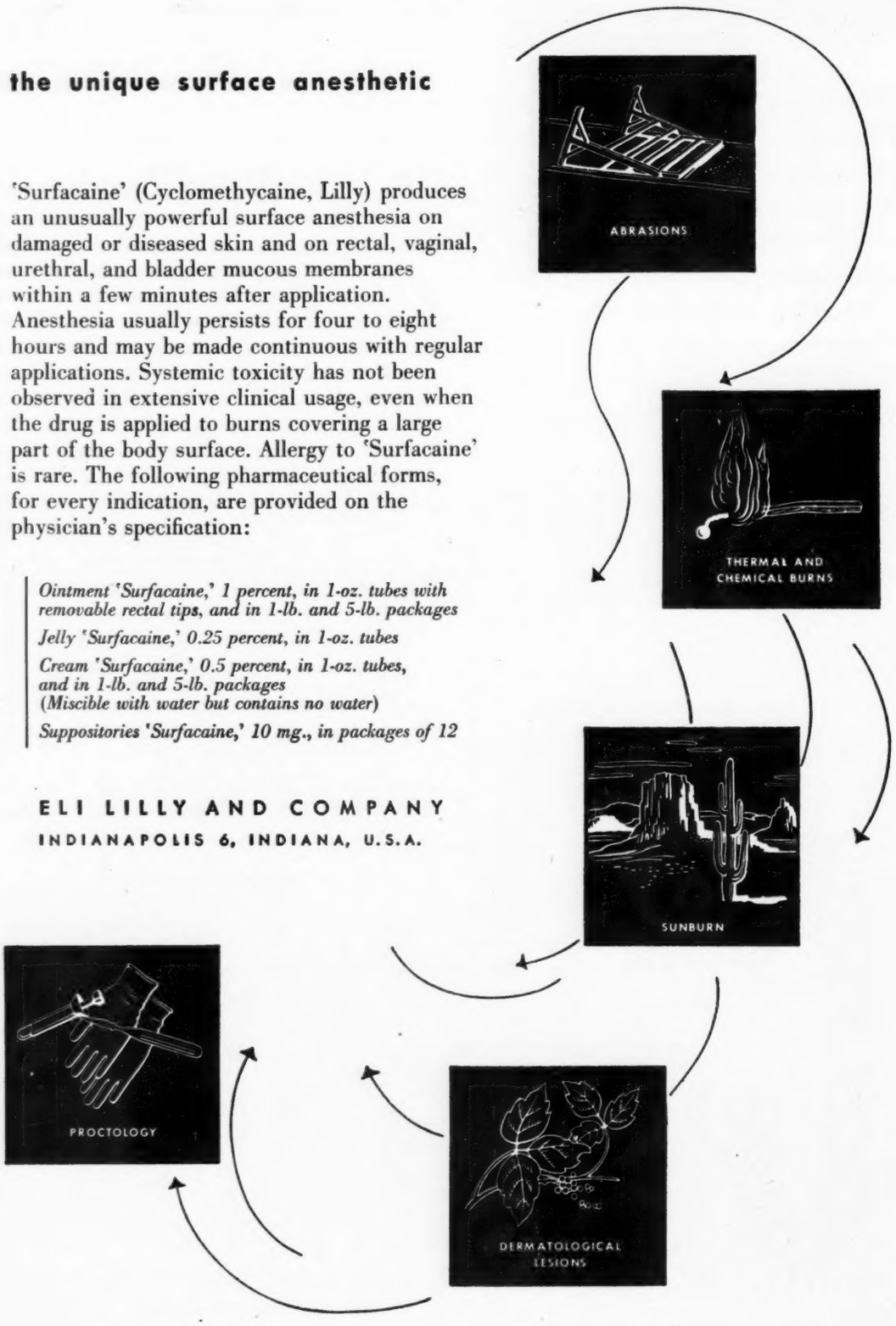

The American Journal of Medicine

VOL. V JULY, 1948 No. 1

Editorial

Retrospect and Prospect, 1948

WITH this issue The American Journal of Medicine enters upon its third year of publication. The occasion seems appropriate for a brief commentary on the problems of the preceding year and on the plans for the future.

A major editorial problem of the past year was how to deal with the flood of manuscripts submitted for publication. At the time the Journal was founded it was appreciated that additional vehicles for publication were needed but it was not anticipated that within so short a period the Journal would suffer an embarrassment of riches in this regard. Many manuscripts of real merit and interest had to be turned away. Despite this, the Journal has a large backlog of papers awaiting publication; of these the original investigations, studies of important new drugs, instructive clinical reports, and the like, are given precedence at the discretion of the editor. To expedite publication further and thus ensure current interest, the publishers have undertaken to increase the capacity of the Journal by adding thirty-two pages, as will have been noted in recent issues. This step and the continued fine format and typography are a warrant of the intention to maintain the highest standards.

The content of the Journal continues to reflect the editorial aims previously set forth: to aid in making generally available the results of sound clinical investigation, and to exploit the teaching opportunities of the Journal as an instrument for postgraduate medical instruction. By reporting both the research and teaching programs of our large medical schools and clinics, the Journal seeks to reflect the main lines of current medical endeavor and faithfully to represent contemporary medical thought and practice.

As already indicated, there has been no difficulty in obtaining a sufficient number of experimental and clinical studies of high caliber and of the desired character and scope. These studies come from all parts of the country. Many are the work of younger men evincing great talent, capacity and thorough training; surely, an indication that American medicine is in a healthy and vigorous state, and a happy augury for the future.

Much time and thought were given to development of the teaching program of the Journal. The principal components of this program continue to be the various Conferences, which bring to the reader discussions of topics of current interest directly from the classrooms of university hospitals. The editors of these Conferences, the Cornell Conferences on Therapy, Columbia Combined Staff Clinics, Washington University Clinico-pathologic Conferences, Harvard Conferences on Psychosomatic Problems, have been unsparing of their time and energy to make these effective teaching exercises of sustained interest. The Journal is privileged to continue publication of the Conferences through the coming year.

Two series of seminars appeared in the pages of the Journal in the course of the past year, one on thromboembolism, the other on hypertension—timely subjects, dealt with fairly and authoritatively in their

manifold facets. The current issue brings the first of the new series, on the use of protein hydrolysates.

The November, 1947 and May, 1948 issues presented detailed symposia on allergy and on aviation medicine, respectively. For the coming year the Journal has scheduled symposia of similar high caliber on syphilis and poliomyelitis. Reviews and editorials on a variety of appropriate subjects have appeared and will continue to appear in each issue. For all these it has been possible to enlist the aid of authorities in their respective fields and they have given generously of their time and energy to strengthen the teaching program of the Journal.

To further the development of the younger societies for clinical investigation, the Journal has undertaken to publish the scientific proceedings of the American Federation for Clinical Research, the Western Society for Clinical Research and the Southern Society for Clinical Research. These proceedings offer a varied program of much current interest and have proved a welcome addition to our pages.

It is most gratifying to the editorial board and to the publishers to note that these efforts have made for The American Journal of Medicine, even in this brief period, a place of respect and affection among the established medical journals of the country. The list of subscribers and readers has already reached a point ensuring stability of the Journal and maintenance of the present high standards in content and format. The Journal owes this success to the loyal support of its many friends and every effort is being made to justify and increase their confidence in its future.

ALEXANDER B. GUTMAN, M.D.

Clinical Studies

Antistreptolysin "O"*

A Study of This Antibody in Health and in Hemolytic Streptococcus Respiratory Disease in Man

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HEMOLYTIC streptococci responsible for nearly all primary infections, particularly of the respiratory tract in human beings, are members of a single serologic group designated by the letter "A."[1] The members of this group form at least two hemolysins.

One, streptolysin "S," is formed *in vitro* in the presence of serum. It is a very toxic, unstable substance and has been identified with the previously described Weld hemotoxin. The hemolysis of blood agar plates is caused by streptolysin "S." When injected into animals, this substance causes death in association with severe intravascular hemolysis. No rôle in human disease has been assigned to this product of the streptococci but it does stimulate the production of a neutralizing antibody in infected persons which has not been widely investigated.[2,3,4]

Streptolysin "O" is the heat and oxygen labile hemolysin that is produced *in vitro* in serum-free broth.[5] Its hemolytic action can be demonstrated only when it is in the reduced state. Differences of opinion exist as to its effect on living animals. Todd has shown that the lethal substance in filtrates of cultures of group A hemolytic streptococci when highly purified is heat and oxygen labile, indicating that it is streptolysin "O."[6,7] This observation has been fully confirmed in this laboratory. Harris,[8] on the contrary, has described a heat and oxygen stable, lethal substance in somewhat similar preparations which Foley[9] suggested might well be Dick toxin. Streptolysin O is a cardiotoxin for the frog heart,[10] a leucocidin,[11] and is not the erythrogenic material.[12]

This toxin is not known to be etiologically responsible for any of the manifestations of the disease caused by hemolytic streptococci in man, but does stimulate the formation of an easily measurable antibody in infected human beings which has been extensively studied.[13] Nearly all investigators have demonstrated that the serum concentration of antistreptolysin O is increased after infection by group A streptococci, in acute rheumatic fever and in glomerulonephritis, and that normal titers are the rule in rheumatoid arthritis and periarteritis nodosa.[14–22]

Coburn[23,24,25] has advanced the hypothesis that there is an intimate relationship between the nature of the antistreptolysin O response following streptococcal respiratory disease and the development of the rheumatic state. This argument has not been supported by all subsequent work[26,27,28] although a similar observation has been made by Green.[29]

Few of the earlier studies of the mechanics of the antistreptolysin O response involved serial antibody determinations in a large

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† This investigation was conducted under the auspices of the Commission on Hemolytic Streptococcal Infections, Army Epidemiological Board, Office of the Surgeon General, United States Army, Washington, D. C. Dr. Wesley W. Spink and Dr. Paul J. Boisvert participated in the clinical phases of this investigation.

group of infected individuals who were under close observation over considerable periods of time. This paper is the report of such an investigation conducted in military personnel.

CLINICAL MATERIAL

This report is based principally on a detailed study of 335 cases of group A hemolytic streptococcus sore throat in male military personnel who were admitted to a large station hospital. Patients were selected for inclusion in the study group on the basis of clinical and bacteriologic criteria that have been presented in great detail elsewhere.[30] Infection by group A hemolytic streptococci was established in 303 cases by the application of several immunologic procedures which were described in another report.[31] Serial antibody determinations were available in 256 of these during the fourth week after the onset of acute respiratory infection. Most of the analyses in this paper will be based upon data collected from these 303 examples of proved streptococcal disease. Complete descriptions of the nature of the respiratory infections and of the suppurative and non-suppurative complications that frequently followed have been presented in a series of papers.[30,32,33,34]

METHODS

Sera for antibody determinations were aseptically collected routinely on the second hospital day, again between the eighth and tenth, and between the twenty-first and twenty-eighth days of illness, and at weekly intervals thereafter in a selected group of cases.

The antistreptolysin* titers of the sera were measured by a method previously described.[35] The lysin was standardized against human sera of known antibody content obtained from Dr. Rebecca Lancefield. The method was later rechecked with rabbit serum containing 20,000 units per ml. which was supplied by Dr. E. W. Todd. No alteration in the originally obtained values was necessary.

A significant antistreptolysin response in this report has been defined as one in which the decrement of diluted serum in the system was 0.4 ml. or more. This corresponds to two dilution tubes as the method is performed in this laboratory.

THE ANTIBODY

Antistreptolysin is among the most satisfactory of all antibodies for laboratory study. The methods for its quantitation are simple and yield results that are more readily reproduced than those ordinarily obtained with immunologic procedures. Large numbers of sera may be titrated with ease. No loss of antibody content has been noted in sera stored aseptically at 2° to 3°C. over a period of two to three years.

The distribution of this immune substance among several of the plasma fractions of Cohn, as prepared from a single pool of plasma, is shown in Table 1. The antibody is, like many others, associated with the gamma globulin and is present in the various fractions in concentrations roughly comparable to the amount of this protein present in each. An increase in gamma globulin has been previously observed in association with an antistreptolysin response during recovery from group A hemolytic streptococcal infection.[36]

Antistreptolysin crosses the placenta and appears in the fetal blood in amounts that are often greater than those present in the maternal blood.[37,38] Great individual differences exist between various mothers and infants in the relative concentrations of antistreptolysin in the serum of the newborn child.[39] It is possible that these observations give information as to the permeability of the placenta to antibody, a subject of interest to students of Rh isoimmunization of the fetus.

The serum antistreptolysin concentration of human beings suffering from renal disease associated with the nephrotic syndrome is regularly low.[40,41] Unpublished observations[41] reveal that urinary proteins obtained

* The terms, streptolysin and antistreptolysin, as used throughout the remainder of the paper refer to streptolysin "O" and antistreptolysin "O."

from such persons by dialysis and dehydration from the frozen state contain considerable amounts of this antibody. In four studied cases the daily excretion of antibody was 3,840, 1,250, 860 and 38 units per a twenty-four-hour period. The serum antistreptolysin titers in each instance were 50, 24, 12 and less than 5 units per ml., respectively. The amount of antibody in the urine was roughly proportional to the serum concentration. The low serum antistreptolysin titers in the presence of heavy proteinuria are presumably the result of loss of this substance in the urine.

TABLE I
CONCENTRATION OF ANTISTREPTOLYSIN "O" IN VARIOUS PLASMA FRACTIONS (COHN)

	Plasma Fraction							
	I	II	III[2]	IV[1]	IV[3-4]	IV[6]	IV[7]	V
Concentration of gamma globulin* (per cent)	10	95	27	1	0	0	5.5	0
Concentration of antistreptolysin "O" in units per Gm. of dry protein	100	6,600	660	100	0	0	100	0

* As determined by electrophoretic analysis.

Interesting investigations into the nature of the process leading to inactivation of streptococcus hemolysin by antistreptolysin may be suggested but none have been undertaken. Unpublished studies made in this laboratory have demonstrated that a non-hemolytic formalin toxoid prepared from streptolysin will neutralize the antihemolytic effect of the antibody with the same facility as the untreated lysin in the oxidized or reduced state.

ANTISTREPTOLYSIN "O" TITERS IN HEALTH

It has been shown previously that the range of antistreptolysin titers of sera from healthy human beings varies with the age[26,38,42] and geographical area of residence of the subjects.[43] The antibody levels of sera obtained from 588 young male soldiers at the onset of an acute respiratory illness have been analyzed. It is believed that these titers are representative of those in the population of the study group as a whole. No relationship between the duration of military service or the length of residence at the study post and the mean antistreptolysin titer was demonstrated. The data upon which this statement is based have been omitted.

The pre-military residences of the members of the study group have been compared with the antistreptolysin titer and the data summarized in Table II. The mean antibody levels varied greatly from area to area, being lowest in the Southwest and Southeast and highest in the Middle West and Far West. Statistical analysis reveals that Zones 7 and 11 varied significantly from the group as a whole. A small number of additional comparisons presented at the bottom of the table demonstrate that the differences between the mean titers in several areas are also significant.

The range of titers in this group of 588 males of military age, whose pre-military residences had been distributed over the whole United States, is presented in Table III (Columns 7 and 8). Data derived from three additional investigations of somewhat similar scope in adults and children are included. The first was conducted one year after the work described in this paper among a similar population in a military establishment (Columns 9 and 10).[44] The subjects for the second study in 1934 were young civilian adults living in various parts of the United States (Columns 11 and 12).[43] The third includes healthy children and older adults who were studied in the

TABLE II

DISTRIBUTION OF ANTISTREPTOLYSIN "O" TITERS IN HEALTHY HUMAN BEINGS

Antistreptolysin Titer (units per ml. of serum)	Present Study											
	Children Age 1.5–3 years		Children Age 5–12 years		Adults Age 40–60 years		Military Personnel		Lemon and Hamburger		Coburn and Pauli	
	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total	No. of Cases	% of Total
Mean titer	<12		238		33		117		91		104	
12 or less	17*	94.4	23	22.7	27	61.3	94	16.0	28	14.5	0	0.0
50	0	0.0	11	10.9	13	29.5	128	21.8	66	34.1	89†	23.3
100	0	0.0	9	8.9	1	2.3	82	13.9	30	15.8	160	42.1
125	0	0.0	7	6.9	2	4.5	120	20.4	34	17.6	63	16.5
166	1	5.5	15	14.8	1	2.3	97	16.4	28	14.5	42	11.1
250	0	0.0	6	5.9	0	0.0	42	7.1	5	2.5	15	3.9
333	0	0.0	11	10.9	0	0.0	12	2.0	2	1.0	9	2.3
500	0	0.0	6	5.9	0	0.0	8	1.4	0	0.0	3	0.8
625	0	0.0	6	5.9	0	0.0	6	1.0	0	0.0	0	0.0
833	0	0.0	4	3.9	0	0.0	0	0.0	0	0.0	0	0.0
1,250	0	0.0	3	2.9	0	0.0	0	0.0	0	0.0	0	0.0
Total	18	100.0	101	100.0	44	100.0	589	100.0	193	100.0	381	100.0

* Titers less than 12 units in 16

† Values less than 50 units per ml. included here

TABLE III

RELATIONSHIP OF PRE-MILITARY RESIDENCE TO THE ANTISTREPTOLYSIN "O" TITER

Zone*	Region	No. of Cases	Mean Antistreptolysin Titer (units per ml.)	Standard Error	P—Mean All Cases
1	New England	56	110	±14	>.5
2	New York	66	105	±13	.4
3	North Atlantic	61	127	±11	.4
4	Middle Atlantic	37	99	±17	.4
5	Border	49	108	±15	>.5
6	Southeast	45	96	±14	.2
7	Southwest	40	82	±11	<.01
8	Great Lakes	137	130	± 9	.2
9	Middle West	47	150	±19	.1
10	Rocky Mountain	7	110	±24	>.5
11	Far West	43	150	±11	<.01
All Cases		588	116	± 4	

* Zone 1: Me., N. H., Vt., Mass., Conn., R. I.
Zone 2: N. Y.
Zone 3: Pa., N. J., Del., Md.
Zone 4: Va., N. C., S. C.
Zone 5: W. Va., Ky., Tenn.
Zone 6: Ga., Fla., Ala., Miss., La., Ark.
Zone 7: Tex., Okla., Ariz., N. Mex.
Zone 8: Ohio, Ind., Ill., Mich., Wis., Minn.
Zone 9: N. Dak., S. Dak., Nebr., Kan., Iowa, Mo.
Zone 10: Mont., Idaho, Wyo., Col., Utah
Zone 11: Calif., Wash., Ore.

Zone 9 compared with Zone 7	P = <.01
Zone 9 compared with Zone 6	P = .02
Zone 9 compared with Zone 4	P = .05
Zone 8 compared with Zone 7	P = .01
Zone 8 compared with Zone 6	P = .04
Zone 3 compared with Zone 7	P = <.01

San Francisco area between 1940 and 1947 (Columns 1, 2, 3, 4, 5 and 6).

The results obtained in the three young adult groups, remote from one another in time and space, are quite similar. (The values of Lemon and Hamburger[44] are lower because hemolytic streptococcus carriers were excluded.) Antistreptolysin titers in children under three years of age were very low. Between the ages of five and fifteen there was a sharp increase in the antibody concentrations, the mean titer for all subjects in this group being nearly twice as great as in young adults.

The percentages of young men whose antibody level was 100 units per ml. or less were 51.7, 64.4 and 65.3 for the three groups, whereas 11.5, 3.5, and 7.0 per cent had antistreptolysin titers of 250 units per ml. or more. After forty years of age the levels were uniformly low.

Comment. The concentration of antistreptolysin in the sera of healthy human beings varies with the age and geographic area of residence of the population under study. Antibody levels are very low after the first months of life, rise constantly through the first decade and then decline with advancing age. These results are in accord with the established frequency of occurrence of hemolytic streptococcal respiratory infection in the several age groups.

The antistreptolysin titers of persons living in southern United States, where the incidence of streptococcal disease is low, are less than in those residing in the north where infection by these organisms is a common event. These observations demonstrate that a correlation exists between the frequency of infection by group A streptococci in a group of human beings and the range and mean antistreptolysin titers of their sera.

It is not presently possible to draw any finite conclusions in regard to the relationship between the absolute rate of infection and the mean antistreptolysin titer. Because the measurement of this antibody is extremely simple and because the method can be well standardized, a program could be readily planned which should give satisfactory information in regard to the relative incidence of group A hemolytic streptococcal respiratory infection in various populations.

Statistically adequate numbers of sera should be collected from individuals of comparable age groups in various areas of this country and elsewhere during the same season of the year. The early fall, when streptococcal infections are occurring infrequently in most communities in the Northern Hemisphere, would be an appropriate time. The sera could be shipped to a central laboratory for titration since antistreptolysin is quite stable.

A study of this sort by an agency of national or international scope would yield information of the greatest value in regard to the relative incidence of group A hemolytic streptococcal infections throughout the area under investigation. Mote and Jones have demonstrated the usefulness of such a technic in estimating the rate of occurrence of infection by these organisms in six groups of human beings in a variety of environments.[26]

Important inferences in regard to the ecology of group A hemolytic streptococci and the epidemiology of infection caused by them may be drawn from these data. The sera of 85 per cent of older children and young adults contains 50 or more units of antistreptolysin per ml. Since antibody levels during the first two years of life are much lower than this, it is evident that clinical or inapparent infection by hemolytic streptococci has occurred in nearly every person residing in the United States. These facts emphasize the universality of infection by these organisms.

Any attempt to establish a "normal" range of values for the titer of antistreptolysin in man is meaningless unless the age and geographic area of the study group is defined. An antibody level of 250 units or more in a young adult strongly suggests that a hemolytic streptococcal infection has been a relatively recent event. Different standards must be applied in infancy, childhood,

middle and old age. The data of Mote and Jones[26] may be used for the first twenty years of life in New England and certain of the information contained in this report for the United States as a whole and for the San Francisco area.

summarized graphically in Figure 1. The antibody levels at the onset of the acute streptococcal respiratory infection and those obtained eight to ten and twenty-one to twenty-eight days later are recorded. Therapeutic regimens, including the administra-

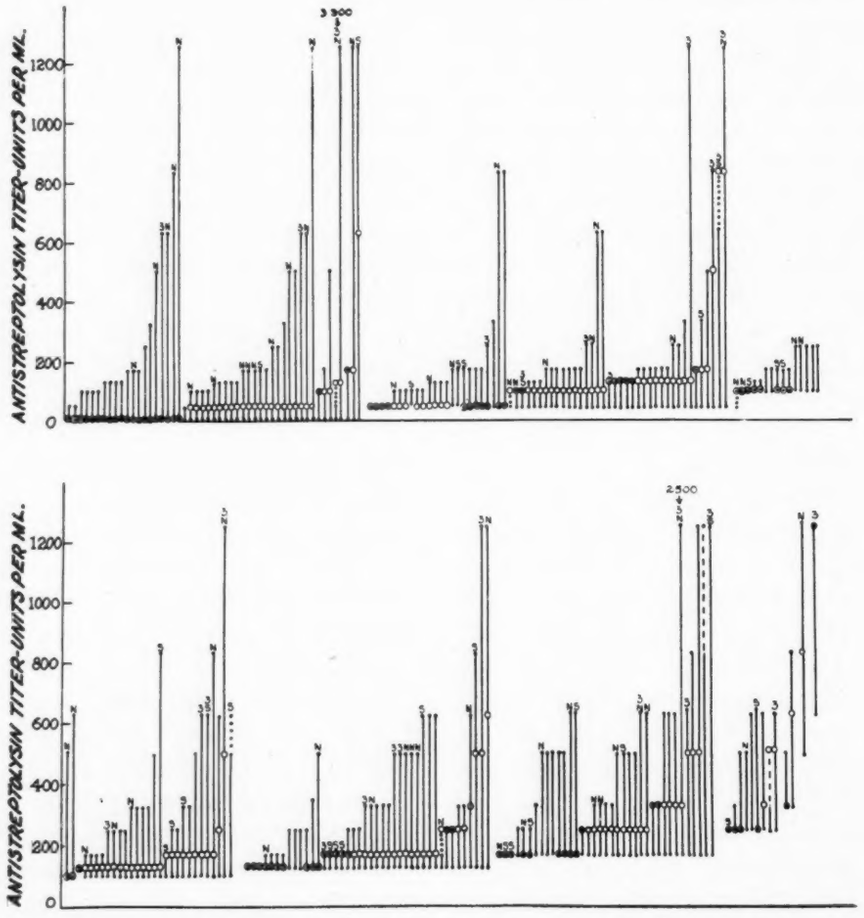

FIG. 1. Lower dot indicates initial antibody level; circle indicates antibody level on eighth to tenth day of illness; upper dot indicates antibody level during fourth week of illness; superscript "N" indicates a non-suppurative complication; superscript "S" indicates a suppurative complication; superscript "3" indicates infection by a streptococcus of type 3.

Isolated determinations of the antistreptolysin titer should be interpreted with the greatest caution when evaluating the relationship of hemolytic streptococcal infection to various pathologic states.

ANTIBODY MECHANICS

Most of the essential information derived from the study of the antistreptolysin response in 256 cases of proved group A hemolytic streptococcus infection has been

tion of penicillin, sulfadiazine and sodium salicylate in various amounts and combinations, were instituted in many of the patients. These procedures have been ignored throughout this paper since previous analyses demonstrated that none greatly altered the natural history of the disease or the antibody response which accompanied it.[33,45,46]

Certain generalizations may be made from the data. An increase in antibody

occurred in approximately 95 per cent but was significant as defined in this paper in only 87.5 per cent of these patients. The accuracy of the method for determination of the antibody is exemplified by the fact that a fall in antistreptolysin titer from that obtained at the onset was never detected.

An increment in antibody concentration was discovered in approximately 55 per cent and was significant in 43 per cent of all patients by the tenth day of illness. The maximum titer was reached at this time in only 9 per cent of cases in whom any response was noted.

Great individual differences were observed in the magnitude of the antistreptolysin response as indicated by antibody levels present during the fourth week which were probably nearly maximal in most cases. (Figs. 2 and 3.) The attainment of very high titers at this time was most often associated with infection by a streptococcus of type 3 or with the development of a suppurative or non-suppurative complica-

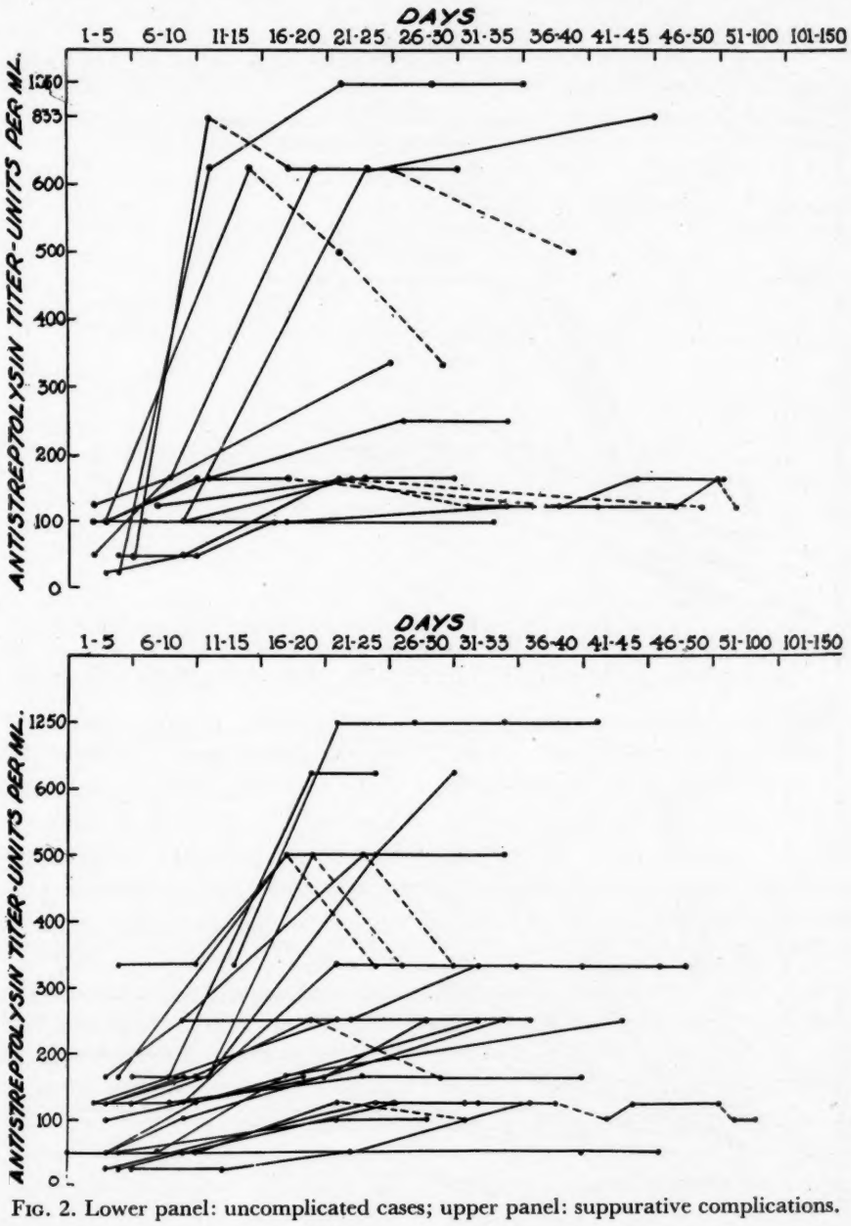

FIG. 2. Lower panel: uncomplicated cases; upper panel: suppurative complications.

tion. Fifty-two of seventy-nine, or 66 per cent, of patients in whom the peak antistreptolysin titer was 500 or more units per ml. fell into one of these three categories whose total number made up only about 40 per cent of all cases. Titers as great as this were attained by 53 per cent of patients in whom a non-suppurative complication supervened, but only by 23 per cent of uncomplicated infections not caused by type 3. This potentially important observation will be the subject of additional comment later in this paper.

Only a few of the uncomplicated cases were followed by means of serial antibody determinations after the fourth week. The results obtained as well as those in patients who developed a suppurative complication or a non-suppurative disorder, in which the manifestations were arthritis, fever or carditis, are displayed graphically in Figures 2 and 3. These figures again demonstrate the

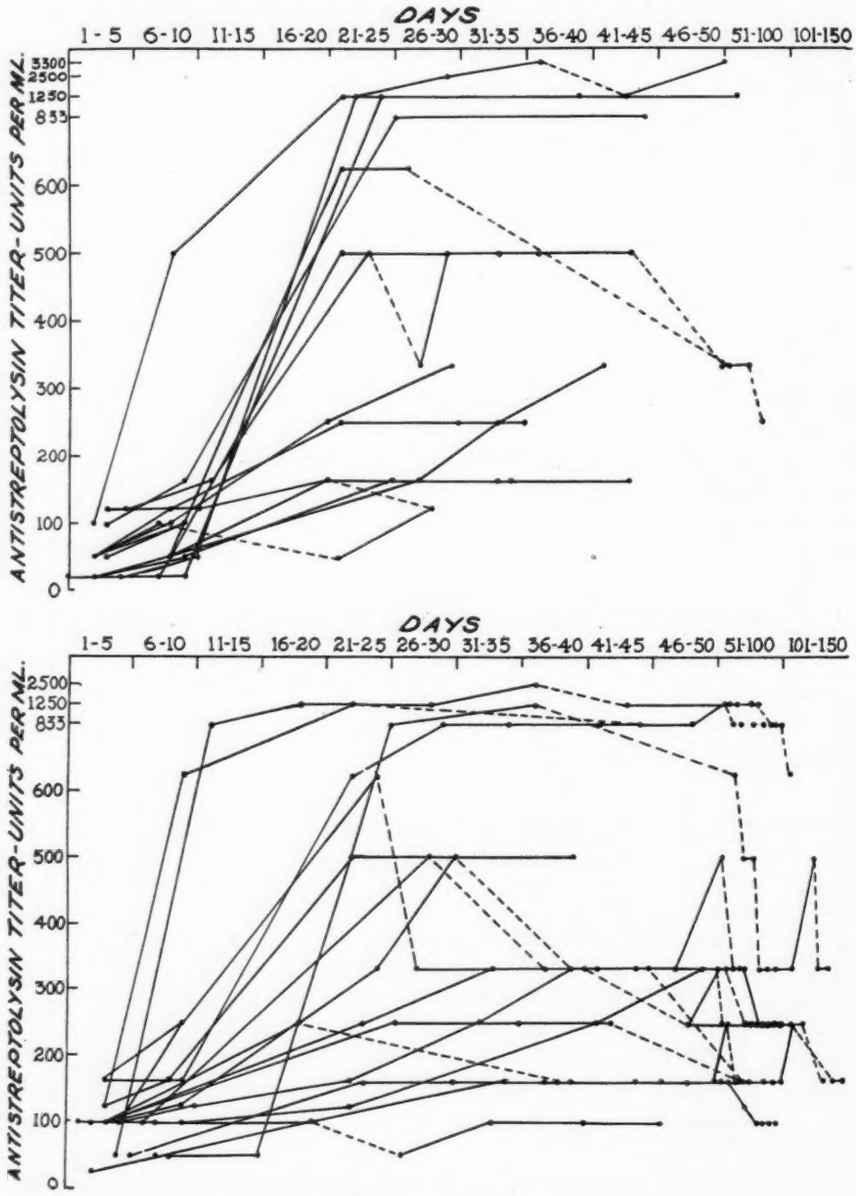

FIG. 3. Upper panel: non-suppurative complications—carditis and late fever; lower panel: non-suppurative complication—arthritis.

quantitatively more vigorous production of antistreptolysin in association with suppurative and non-suppurative complications.

The maximum antibody level was attained by the end of the fourth week in a large majority of the patients followed after this period, irrespective of the presence or absence of complications. The development of arthritis or other non-suppurative disorder was not associated with a slow or delayed antistreptolysin response.

The antibody concentrations, after reaching a peak, were usually maintained for a considerable period of time. Table IV summarizes the information in regard to this point. After the fiftieth day significant declines in the antistreptolysin titer occurred frequently but were not observed in many patients followed for two or more months.

One of the authors has previously stated[47] that the fold increase in antistreptolysin in human beings is greater following infection by group A hemolytic streptococci if the initial antibody titer is low than if it is high. This point of view has been criticized[48] and it has been suggested that the total production of antibody is probably similar at any initial level. Table V confirms this suggestion. The mean quantity of antistreptolysin formed by patients whose titer at the onset varied from 12 to 250 units was comparable.

Information in regard to the apparent antistreptolysin mechanics in relationship to the dilution system used for the measurement of the antibody is presented in this table. It will be observed that an increment in antibody of greater absolute magnitude is required as the initial level becomes higher if a significant response is to be detected. A progressive fall occurred in the frequency of significant increments in antistreptolysin in this group of patients as the antibody titers at the onset of the infection increased. A two-tube response was observed in 100 per cent of patients whose initial level of antistreptolysin was very low and in only 70 to 80 per cent of those in whom large amounts of antibody were present early in the disease. Since the mean production of antibody at all levels is similar, it is clear that the failure to demonstrate a significant response in certain cases is almost entirely the result of the technic used in the measurement of the antibody. The results are similar when any, other than significant, antibody response is considered (last three columns of Table V).

TABLE IV

RELATIONSHIP BETWEEN NATURE OF THE CLINICAL DISEASE AND ANTISTREPTOLYSIN TITER DURING CONVALESCENCE FROM HEMOLYTIC STREPTOCOCCUS SORE THROAT

Antistreptolysin Titer at Follow-up†	Uncomplicated Cases, Day of Follow-up Study*			Suppurative Complications, Day of Follow-up Study*			Non-suppurative Complications, Day of Follow-up Study*					
	30–40	40–50	50+	30–40	40–50	50+	30–40	40–50	50–60	60–70	70–80	80†
Unchanged	10	3	0	7	2	0	18	20	10	7	7	2
Significant increase	1	1	0	0	0	0	5	0	0	0	0	0
One tube increase	5	1	0	1	0	0	11	1	0	0	0	0
Significant decrease	1	0	1	0	0	0	2	0	4	2	1	2
One tube decrease	2	0	2	2	1	0	4	4	5	3	2	3
Total	19	5	3	9	4	0	40	25	19	12	10	7

* Patients not tabulated after that period in which a significant fall in antibody was first observed.
† As compared with titers during the fourth week.

Comment. Certain details of the mechanics of antistreptolysin response in a large number of proved group A hemolytic streptococcus respiratory infections in young adults have been presented.

An increase in antibody was observed in nearly all cases by the fourth week after the onset of the illness and was usually maximal at this time. Frequently a response had occurred by the eighth to tenth day and was often significantly large but rarely maximal. The mean magnitude of the increase in antibody was shown to have been comparable at all initial levels of antistreptolysin. The dilution system used in the measurement of this immune substance resulted in a progressive decline in the incidence of significant responses as the titer of antibody at the onset of the illness became larger.

Great individual differences in the magnitude of the antistreptolysin response were exhibited by different patients. The largest increments in antibody were observed in men infected by strains of type 3, or in those in whom suppurative or non-suppurative complications supervened.

Little information was obtained in regard to the persistence of antistreptolysin in the serum after the first month. Decrements in antibody concentration were not uncommon during the following thirty days but were not observed in many patients.

RELATIONSHIP OF INITIAL ANTISTREPTOLYSIN "O" TITER TO THE NATURE OF THE CLINICAL DISEASE

A previous study has indicated that the concentration of antistreptolysin in the serum of patients at the onset of hemolytic streptococcal respiratory disease bears no relationship to the natural history of the acute illness.[49] This observation has been fully confirmed during the investigation described in this report. The initial antistreptolysin titer could not be correlated with the degree of abnormality of physical signs, height or duration of fever or the initial or follow-up erythrocyte sedimentation rate. The data on which this statement is based have been omitted. Normal or moderately elevated total leukocyte counts were associated with higher mean antistreptolysin levels than were high counts when antibody determinations and clinicopathologic observations were made early in the acute illness. (Table VI.)

The differences between the two lower categories of total leukocyte counts and the third (13,000 to 15,999) and fourth (16,000 or more) are significant (P equals .01 to .02). Inspection of the distribution curves of the antibody levels from which these means were derived suggests that the variations just described may not be valid biologic correlations.

TABLE V

RELATIONSHIP BETWEEN INITIAL ANTISTREPTOLYSIN "O" TITER AND FREQUENCY AND MAGNITUDE OF ANTIBODY RESPONSE

Initial Antistreptolysin Titer (units/ml.)	Ml. of Diluted Serum in System	No. of Cases	Mean Increase in Antibody (units/ml.)	Increment Required for Significant Response (units/ml.*)	Significant Responses		Increment Required for Any Detectable Response (units/ml.)	No Response	
					No.	%		No.	%
12	.8	51	277	38	51	100.0	38	0	0.0
50	.2	62	216	75	57	91.9	50	4	6.4
100	1.0	44	244	66	39	88.8	25	2	4.5
125	.8	41	271	125	29	70.7	41	3	7.3
166	.6	38	377	167	30	78.7	84	4	10.5
250	.4	9	269	250	6	66.6	83	1	11.1

* A decrease of .4 ml. or more of diluted serum in the system.

The differences between the two lower categories of total leukocyte counts and the third (13,000 to 15,999) and fourth (16,000 or more) are significant (P equals .01 to .02). Inspection of the distribution curves of the antibody levels from which these means were derived suggests that the variations just described may not be valid biologic correlations.

The amount of antistreptolysin present in the serum at the onset of acute hemolytic streptococcus sore throat has been compared with the frequency of development of suppurative and non-suppurative complications.[32,33,34] (Table VII.) The distribution of

TABLE VI

RELATIONSHIP BETWEEN INITIAL ANTISTREPTOLYSIN TITER AND TOTAL LEUKOCYTE COUNT

Initial Total Leukocyte Count (cells per cu. mm.)	No. of Cases	Mean Antistreptolysin Titer (units per ml.)	Standard Error
9,000 or less.....	69	104	±10
10,000 to 12,999.....	82	104	±10
13,000 to 15,999.....	68	73	± 7
16,000 or more.....	75	93	± 6

and mean titers in patients who recovered uneventfully and in those in whom otitis media, peritonsillar abscess and sinusitis were diagnosed were similar.

The late appearance of arthritis, fever and carditis, as exemplified by the presence of an abnormal electrocardiogram, has been regarded as a manifestation of a common pathologic process.[32,34] The mean initial antistreptolysin titer in forty individuals in whom one of these complications appeared during convalescence was lower than the value obtained in uncomplicated cases and in those with suppurative complications. Further analysis demonstrates that antibody levels were very low in patients who developed late fever and carditis and were high in arthritics. Four persons in the latter group had initial antistreptolysin titers of less than 100 units per ml. The involvement of the joints was minimal in three, and the fourth suffered a series of reinfections by strains of hemolytic streptococci of different serologic types before arthritis became manifest.

Comment. If streptolysin "O" has a rôle in the pathogenesis of any of the manifestations of the acute suppurative phase of group A hemolytic streptococcus sore throat, a correlation should exist between the concentration of neutralizing antibody (antistreptolysin "O") at the onset of the illness and the severity or extent of those manifestations of the disease process caused by this toxin. This and previous investigations have established the fact that no such relationship can be demonstrated. Further-

TABLE VII

RELATIONSHIP BETWEEN INITIAL ANTISTREPTOLYSIN "O" TITER DURING THE ACUTE PHASE OF STREPTOCOCCAL SORE THROAT AND DEVELOPMENT OF COMPLICATIONS

Antistreptolysin O Titer (units/ml.)	No. of Cases*	Uncomplicated	Suppurative Complications	Non-suppurative Complications			
				Arthritis	Late Fever	Carditis	Total
12 or less	51	39	2	1	6	3	10
50	71	56	6	3	3	3	9
100	47	30	8	8	1	0	9
125	48	36	5	3	2	2	7
166	34	26	5	2	0	1	3
250	13	10	2	1	0	0	1
333	3	2	0	0	1	0	0
500	2	2	0	0	0	0	0
625	1	1	0	0	0	0	0
Mean titer		98	109	107	70	67	79
Total cases	270	202	28	18	13	9	39

* Twenty-one cases in which a variety of probable or possible non-suppurative complications occurred[34] have been omitted.

more, certain streptococci that produce abnormally large amounts of hemolysin do not cause disease differing in any respect from that resulting from infection by the strains forming less of this substance.[33] These observations suggest that it is proper to dismiss this substance from the armamentorium of toxins produced by group A hemolytic streptococci that are known to affect human tissues directly.

Arthritis and late fever, with or without carditis, and the latter complication alone have been regarded as non-suppurative complications of hemolytic streptococcus respiratory infection and the pathogenesis of all has been believed to be similar. An immunologic difference between arthritic and non-arthritic poststreptococcal disease has been demonstrated.[50] Involvement of the joints was much more frequently associated with the presence initially or development during convalescence of a precipitating antibody reacting with a component of acid extracts of group A streptococcal cells.

The present investigation has revealed another dissimilarity between these disorders. The initial antistreptolysin titers were higher in patients who were later to develop arthritis than in those in whom fever, with or without carditis or carditis alone, were manifestations of the complication. This relationship was particularly striking if only severe or moderately severe arthritic cases were considered.

The number of patients with complications in these three categories is small but the results become more impressive when it is realized that the initial antistreptolysin titer was less than 100 units per ml. in 66 per cent of uncomplicated and 68 per cent of cases in which non-arthritic, nonsuppurative complications appeared. Antibody concentrations as small as this were never discovered in the early sera collected from patients who developed marked arthritis unless reinfection by new types of hemolytic streptococci occurred (one case).

This observation adds weight to the argument previously offered[32] which stated that all forms of poststreptococcal nonsuppurative disease were the result of an immunologic reaction, possibly involving sensitization by preceding contact with the organism. The suggestion was made that non-arthritic disorders frequently followed an isolated infection by a single type, but that the production of arthritis probably required multiple, relatively closely spaced infection by hemolytic streptococci leading to an advanced degree of hypersensitivity. The moderately elevated antistreptolysin titers discovered in men at the onset of streptococcal disease followed by arthritis indicate that these patients had undergone infection by these organisms more recently than the remaining patients in whom the joints were not involved.

RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO NATURE OF CLINICAL DISEASE

The data obtained from the study of 256 of the 303 proved cases of group A hemolytic streptococcus sore throat were analyzed to determine the relationship between the frequency and magnitude of antistreptolysin response and the nature of the acute illness and complications which often followed it. Patients were selected for inclusion in the group only if follow-up antibody determinations were made during the fourth week after the onset of infection.

Data obtained from the whole group of 256 cases were used for the determination of the frequency of antibody response. The mean antistreptolysin increase was calculated from the results in 237 patients in whom any increment in antibody occurred. In several instances this was not a significant response. Analyses were made with infections caused by streptococci of type 3 included and excluded. The latter procedure was performed because the magnitude of antistreptolysin response associated with infection by organisms of this type was usually exaggerated and, in part, obscured well defined trends in magnitude of antibody response which will be described.

Acute Suppurative Disease. Close relationship between certain manifestations of the acute suppurative phase of hemolytic streptococcus sore throat and the absolute magnitude but not the frequency of antistreptolysin response has been demonstrated. A progressive increase occurred in the mean amount of antistreptolysin formed as the maximum temperature became greater (Table VIII) or more prolonged. (Table IX.)

The differences were highly significant statistically when maximum temperature was considered. Significance was obtained in the analysis pertaining to duration of fever only when the categories including patients with a very short febrile illness were compared with those in whom elevated temperatures had persisted for six or more days.

The magnitude of antistreptolysin response varied in an irregular way (Table X) with the initial erythrocyte sedimentation rate, but patients whose initial rate was less than 20 mm. per hour formed significantly less antibody than did the group as a

TABLE VIII

RELATIONSHIP OF MAXIMUM TEMPERATURE TO FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE

Maximum Temperature	Frequency of Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response							
	No. of Cases	Significant Response		All Cases with Any Increase	Mean Increase (units/ml.)	Standard Error	All Cases Except Type 3 with Any Increase	Mean Increase (units/ml.)	Standard Error	P* 98.6–99.9	P* 100.0–100.9
		No.	%								
Afebrile–99.9	17	13	81.3	16	132	±29	16	132	±29		
100.0–100.9	22	19	86.4	20	193	±43	17	151	±39		
101.0–101.9	52	44	84.6	46	273	±34	43	257	±30	<.01	.2
102.0–102.9	57	51	89.5	55	312	±43	50	275	±41	<.01	.05
103.0 and greater	108	97	89.8	100	312	±36	93	295	±37	<.01	.05–.02
Total	256	224	87.5	237	282	±20	219	260	±19		

* Including type 3

TABLE IX

RELATIONSHIP BETWEEN DURATION OF FEVER AND FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE

Duration of Fever (days)	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response					
				All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody		
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error
		No.	%						
0 to 1	48	39	81.3	46	232	± 32	42	214	± 31
2	63	55	87.3	56	230	± 28	53	224	± 29
3	67	61	91.0	66	300	± 48	57	249	± 47
4	38	33	86.8	32	255	± 40	31	220	± 40
5	15	13	86.6	13	410	±114	13	410	±114
6 or more	25	23	92.0	24	418	± 86	23	388	± 76
All cases	256	224	87.5	237	282	± 20	219	260	± 20

Statistical comparisons of mean increases (type 3 cases included)
P of 0–to–1 compared with 5 equals .2–.1
P of 0–to–1 compared with 6 or more equals .05
P of 2 compared with 5 equals .2–.1
P of 2 compared with 6 equals .05

TABLE X

RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO INITIAL ERYTHROCYTE SEDIMENTATION RATE

Initial Erythrocyte Sedimentation Rate (mm./hr) Westergren	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response						
				All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody			
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error	P* Mean All Cases
		No.	%							
9 or less	22	20	90.9	19	182	±32	18	181	±33	<.02
10 to 19	51	44	86.2	47	208	±33	43	187	±28	.05
20 to 29	51	41	80.4	46	321	±47	41	296	±46	
30 to 39	44	41	93.5	41	251	±33	39	237	±33	
40 to 49	33	30	90.9	30	376	±68	29	349	±65	
50 and more	48	41	85.4	47	323	±64	42	261	±66	
Total	249	217	87.2	230	282	±21	212	259	±20	

* P greater than .1 omitted; type 3 included.

TABLE XI

RELATIONSHIP BETWEEN INITIAL TOTAL LEUKOCYTE COUNT AND FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE

Total Initial Leukocyte Count/ cu. mm.	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response					
				All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody		
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error
		No.	%						
9,000 or less	51	43	84.3	46	282	±45	43	259	±43
10,000 to 12,999	73	66	90.3	66	315	±45	59	281	±45
13,000 to 15,999	59	48	81.3	54	232	±35	51	202	±30
16,000 and more	70	64	91.4	68	286	±35	63	285	±38
Total	253	221	87.4	234	281	±20	216	258	±20

whole. The frequency of response was similar in all categories. No relationship between the maximum initial total leukocyte count and the incidence or size of the antistreptolysin response was discovered. (Table XI.)

cases but the variations were not statistically significant. (Table XIII.)

Non-suppurative Complications. A considerable number of hemolytic streptococcus respiratory infections in this study group initiated pathologic processes apparently

TABLE XII

RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO FOLLOW-UP (4TH WEEK) ERYTHROCYTE SEDIMENTATION RATE

Follow-up Erythrocyte Sedimentation Rate (mm./hr.) Westergren	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin 'O" Response						
				All Cases with Any Increase in Antibody			All Cases Except Type 3 with Any Increase in Antibody			
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	No. of Cases	Mean Increase (units/ml.)	Standard Error	P* Mean All Cases
		No.	%							
9 or less	121	102	84.3	108	190	± 16	102	185	± 16	<.01
10 to 19	53	48	90.5	51	271	± 42	46	217	± 35	
20 to 29	29	25	86.2	27	326	± 52	25	299	± 51	
30 to 39	23	20	86.9	22	398	± 83	19	388	± 85	.1
40 to 49	11	11	100.0	11	375	±127	11	375	±127	
50 or more	19	18	94.7	18	602	±133	16	567	±142	.05–.02
Total	256	224	87.5	237	282	± 20	219	260	± 19	

* P greater than .1 omitted; type 3 included.

The follow-up (fourth week) erythrocyte sedimentation rate was closely correlated with the amplitude of the antistreptolysin response. (Table XII.) Rapid rates at this time were associated with large increases in antibody and the reverse. This phenomenon appears to be associated with the presence of many complicated cases in the group with rapid erythrocyte sedimentation rates at follow-up examination.

Suppurative Complications. The course of twenty-eight cases of hemolytic streptococcus sore throat was complicated by the development of suppurative disorders. Peritonsillar abscess, otitis media and sinusitis were observed. The frequency of antistreptolysin response was slightly greater in these patients and the amount of antibody produced was larger than in uncomplicated

of a non-suppurative nature.[34] Clinical manifestations of these disorders were arthritis with or without fever or carditis (rheumatic fever), late fever with or without carditis, carditis without fever or arthritis, and pneumonitis with or without carditis. Eighteen less clearly defined pathologic states, including late lymphadenitis and prolonged abnormality of the erythrocyte sedimentation rate in the absence of clinical evidence of disease, are segregated in a separate category.

The data summarized in Table XIII reveals that the frequency and magnitude of antistreptolysin response were greater in the presence of all forms of non-suppurative poststreptococcal disorders than in uncomplicated cases.

The variation in total antibody produc-

tion was of statistical significance only in the groups including patients suffering from late fever and miscellaneous disorders. When all non-suppurative disorders were considered together, a similar significant statistical result was obtained.

(Case 7),[34] and was insufficiently great to be significant in additional examples of arthritis, late fever and carditis (one case in each category). These and related complications occurred in many other patients in whom the increment in antistreptolysin was

TABLE XIII

RELATIONSHIP OF FREQUENCY AND MAGNITUDE OF ANTISTREPTOLYSIN "O" RESPONSE TO COMPLICATIONS OF HEMOLYTIC STREPTOCOCCUS SORE THROAT

Type of Complication	Frequency of Significant Antistreptolysin "O" Response			Magnitude of Serum Antistreptolysin "O" Response in All Cases with Any Increase in Antibody			P-Mean Uncomplicated Cases
	No. of Cases	Significant Response		No. of Cases	Mean Increase (units/ml.)	Standard Error	
		No.	%				
Uncomplicated	169	131	72.5	156	210	± 18	
Suppurative complications	28	23	82.1	25	330	± 67	.1
All non-suppurative complications	59	54	91.5	57	434	± 58	.01
Arthritis	18	16	88.9	17	366	± 85	.1
Late fever	13	12	92.4	13	516	±109	.02
Carditis	7	6	85.6	7	344	±170	.5
Pneumonitis	3	3	100.0	3	367		
Other non-suppurative complications	18	17	94.4	20	450	±120	.05
All cases	256	206	80.7	238	282	± 20	<.01

The data presented in Figure 1 demonstrate the vigorous formation of antistreptolysin by many patients in whom non-suppurative complications were observed. Figures 2 and 3 illustrate the course of the antibody response in greater detail and show clearly that peak levels were obtained at a comparable time (fourth week) after the onset of the initial acute hemolytic streptococcus respiratory infection in complicated and uncomplicated cases. The same information is summarized in another form in Table IV.

Although excess production of antistreptolysin by patients in whom non-suppurative complications have supervened is not statistically significant in every category, it is an impressive phenomenon which requires explanation. No antistreptolysin response whatever occurred in one of the most severely ill patients with arthritis only moderately large (Fig. 1) and the maximum titer was less than 200 units per ml. A marked increase in this antibody is not essential therefore in the pathogenesis of these disorders.

It has been demonstrated previously that the frequency and magnitude of antistreptolysin response are related to the severity of the initial suppurative phase of hemolytic streptococcus sore throat. Certain manifestations of acute illness have been analyzed with regard to the subsequent development of complications. (Table XIV.) Inspection of the data reveals that the maximum temperature was lower, the febrile illness of definitely shorter duration and the initial erythrocyte sedimentation rate much less rapid in uncomplicated cases. The average respiratory infection which was to be followed by a suppurative or non-suppurative complication was more severe

than were those in which convalescence was uneventful.

COMMENT

No correlation has ordinarily been demonstrable between the severity of various infectious diseases and the magnitude of antibody response which was associated with them. A previous investigation failed to discover such a relationship in group A hemolytic streptococcus sore throat.[50] The results of the present study differ in that the mean amplitude of the antistreptolysin response was progressively greater as the acute streptococcal respiratory infection became more severe. This phenomenon was most striking when maximum temperature was used as a measure of the severity of the illness, but was quite apparent when comparisons were made between the duration of fever or the initial erythrocyte sedimentation rate and antibody response.

TABLE XIV
RELATIONSHIP OF SEVERITY OF INITIAL ILLNESS TO THE DEVELOPMENT OF COMPLICATIONS

Category	Uncomplicated		Suppurative Complications		Non-Suppurative Complications	
	No.	%	No.	%	No.	%
Duration of fever (in days)						
Afebrile to 1 day	35	22.4	2	8.0	8	14.0
2 days	39	25.0	3	12.0	14	24.5
3 days	45	28.8	6	24.0	14	24.5
4 days	19	12.2	7	28.0	9	15.8
5 days	6	3.8	2	8.0	5	8.8
6 or more days	12	7.7	5	20.0	7	12.3
Maximum temperature						
98.6 to 99.9° F.	15	9.6	1	4.0	0	0.0
100.0 to 100.9° F.	16	10.3	2	8.0	2	3.5
101.0 to 101.9° F.	31	19.9	6	24.0	10	17.5
102.0 to 102.9° F.	30	19.2	6	24.0	19	33.3
103.0° F. and higher	64	41.0	10	40.0	26	45.6
Initial erythrocyte sedimentation rate (Westergren)						
9 or less	18	11.8	0	0.0	1	1.8
10 to 19	38	25.0	1	4.1	9	16.4
20 to 29	35	23.0	3	12.5	8	14.5
30 to 39	25	16.4	5	20.8	11	20.0
40 to 49	16	10.5	6	25.0	8	14.5
50 and up	20	13.2	9	37.5	18	32.7

Another analysis derived from these data has demonstrated that the frequency and magnitude of antistreptolysin response may be a function of the serologic type of the infecting hemolytic streptococcus.[31] This was not responsible for the variations just described since the severity of the illness caused by strains of the various types was similar.[33] Comparable differences in the size of the antistreptolysin response were observed in a monotype food-borne epidemic of hemolytic streptococcus sore throat in which the factor of strain differences could be excluded as a cause for the variations in production of this antibody.[47] Clinical data were inadequate in that study to permit an analysis of antibody mechanics in relationship to the nature of the disease.

The fact that a relationship exists between the severity of acute streptococcal illness and the formation of antistreptolysin was less important and interesting than the demonstration of a similar correlation between the presence or absence of non-suppurative complications and the average magnitude of antibody response. Coburn[23,24] has previously stated that this was the case, but subsequent investigations and a preliminary analysis of present data[50] failed to support his position. However, complete statistical evaluation of information obtained during the study confirms the work of this investigator, as does that of Green.[29]

It is clear that the mean production of antistreptolysin was greater in patients selected on clinical grounds as examples of late non-suppurative complications of hemolytic streptococcal disease than in those in whom prompt and uneventful recovery occurred. Patients were segregated into groups on the basis of the development of arthritis, late fever, pneumonia, carditis or another probable non-suppurative disorder. Excess antistreptolysin formation was demonstrated in all categories. This is to be contrasted with the different situation which was discovered when certain antibacterial precipitating antibodies were studied in these same patients.[50] These substances

were demonstrated with unusual frequency only when arthritis supervened.

The relationship between the augmented production of antistreptolysin in the presence of complications, particularly of the non-suppurative type, demands elucidation which is not possible from the data at hand. The suggestion has been made that these disorders are the result of immunologic reactions, possibly of the anaphylactic type, which are harmful to the tissues. If this be the case, some fraction or product of the hemolytic streptococcus must be the sensitizing antigen and this substance must be common to many types or strains of these organisms. Streptolysin is such a substance and the observations reported here suggest that it and its antibody may be intimately related to the pathogenesis of the non-suppurative poststreptococcal complications. It may be proposed that this toxin is, indeed, the sensitizing antigen itself and that these disorders arise in human beings who form excess amounts of its antibody following infection leading to hypersensitivity of susceptible tissues. A cogent objection to this hypothesis is the fact that arthritic and non-arthritic poststreptococcal disease occurred in individuals in whom no or only minimal increments in antibody were observed and in whom the total concentration of the immune substance remained low. This observation should be contrasted with those of Coburn[24] who maintained that hemolytic streptoccal respiratory infection was not usually followed by the development of a non-suppurative complication in the absence of a large antistreptolysin response.

The possibility must also be considered that the increased production of antistreptolysin in persons who have developed a poststreptococcal complication simply mirrors a generally increased immunologic hyper-reactivity on the part of these patients which led to the development of sensitivity states in which the streptolysin-antistreptolysin system had no rôle. Study of the precipitating antibody previously mentioned did not confirm this suggestion.

Elsewhere[32] it has been noted that a large number of clinical and inapparent reinfections by streptococci of new types occurred in patients who later developed non-suppurative complications and it was possible that these multiple exposures to the infectious agent had resulted in excessive antibody production by these persons. Examination of antibody mechanics in relation to intervals between infections fails to support this hypothesis in more than a few instances. Neither was there an unusually great number of infections by types known to stimulate the formation of large amounts of antistreptolysin.[31]

It has been noted above that the magnitude of the antistreptolysin response was related to the severity of the acute streptococcal disease, and evidence was presented which showed that the frequency of occurrence of severe initial illnesses was high among those men who later developed a non-suppurative complication. It is logical to assume, therefore, that the excess antibody production which was demonstrated in complicated cases was a function of the nature of the inciting infectious processes rather than the result of any of the other mechanisms suggested as explanations of this phenomenon.

No completely satisfactory explanation for the association of non-suppurative poststreptococcal complications and the excessive formation of antistreptolysin has been offered. It is imperative that further investigation of this phenomenon be conducted, since the elucidation of the pathogenesis of these important disease states must be one of the principal goals of all studies of hemolytic streptococcal infection. Methods utilizing fully dialyzable synthetic culture media are now available which permit the preparation of the extracellular products of the streptococcus in a highly purified form.[10] These should be studied for the purpose of devising technics for the separation of streptolysin from the erythrogenic and other substances formed by group A streptococci. Valuable information as to the effect of streptolysin on human tissues

will be obtained when this has been accomplished.

CONCLUSIONS

Antistreptolysin "O" is an immune substance which neutralizes streptolysin "O" *in vitro*. It is contained in the gamma globulin fraction of human serum. Its concentration in the sera of healthy persons and its formation after infection in young adults by group A hemolytic streptocci has been studied. The data have been presented and described in several categories, each of which has been the subject of special comment in the body of the paper.

The amount of this substance in sera obtained from healthy persons varies with the geographic area of residence of the subjects and their age. Antibody levels are very low through the second year of life, rise rapidly through the first decade and then decline. The presence of a wide range of antistreptolysin titers in health indicates that single determinations of the antibody must be interpreted with caution in studies of the etiology of various human diseases.

The mechanics of antistreptolysin response in large numbers of carefully studied examples of proved group A hemolytic streptococcus sore throat have been described. It was noted that an increase in this antibody occurred regularly following infection by these organisms. The amplitude of the response varied from patient to patient but the peak level was reached by the fourth week after the onset of acute illness in nearly all cases.

No relationship between the initial antistreptolysin titer and the nature of the acute suppurative phase of hemolytic streptococcus sore throat was demonstrated. The amount of antibody was moderately increased at this time in patients who later developed arthritis.

A definite correlation between the magnitude of antistreptolysin response, severity of the initial illness and the later development of non-suppurative complications was demonstrated.

These observations and those described in another paper establish immunologic differences between uncomplicated group A hemolytic streptococcus respiratory infection and that which initiates a non-suppurative disorder. An exaggerated mean antistreptolysin response occurred in all clinical categories of the latter group. In addition, the antistreptolysin titer at the onset of the initial streptococcal illness was somewhat higher, and antibacterial precipitating antibodies were present with unusual frequency in patients who later developed arthritis. These facts demand an explanation since one of the primary goals of all studies of hemolytic streptococcal disease must be the elucidation of the pathogenesis of these important late complications of which rheumatic fever is the best known example.

Various interpretations of the phenomenon of excessive antibody formation in association with the appearance of non-suppurative disorders were offered but none was entirely satisfactory. Either the streptolysin-antistreptolysin or the X-anti-X antibody systems may be directly responsible for the hypersensitivity that is presumed to cause non-suppurative poststreptococcal disorders. On the other hand, the abnormal production of these antibodies may mirror an exaggerated immunologic hyper-reactivity of human beings in whom these disease states develop. In the latter case the sensitizing fraction or product of the organism is one whose significance has not been appreciated or it has not yet been discovered.

The preparation of highly purified streptolysin "O," separated from the erythrogenic material and other products of the hemolytic streptococcus, and the study of its properties and effects upon human tissues is a problem urgently requiring investigation.

REFERENCES

1. Lancefield, R. C. Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci. Harvey Lectures, 1940–1941. Baltimore, 1941. Williams & Wilkins Co.
2. Todd, E. W. The differentiation of two distinct serologic varieties of streptolysin, O and S. *J. Path. & Bact.*, 47: 423, 1938.

3. Todd, E. W., Coburn, A. F. and Hill, A. B. Antistreptolysin S titres in rheumatic fever. *Lancet*, 2: 1213, 1939.
4. Herbert, D. and Todd, E. W. The oxygen-stable haemolysin of Group A haemolytic streptococci (Streptolysin S). *Brit. J. Exper. Path.*, 25: 242, 1944.
5. Todd, E. W. Antigenic streptococcal hemolysin. *J. Exper. Med.*, 55: 267, 1932.
6. Herbert, D. and Todd, E. W. Purification and properties of hemolysin produced by group A hemolytic streptococci (streptolysin O). *J. Biochem.* 35: 1124, 1941.
7. Todd, E. W. Lethal toxins of hemolytic streptococci and their antibodies. *Brit. J. Exper. Path.*, 19: 367, 1938.
8. Harris, T. N. A lethal agent produced by the hemolytic streptococcus. *J. Bact.*, 43: 739, 1942.
9. Foley, G. D. Identity of a lethal agent in broth filtrates of hemolytic streptococci with erythrogenic toxin. *Science*, 98: 370, 1943.
10. Bernheimer, A. W. and Cantoni, G. L. The cardiotoxic action of preparations containing the oxygen-labile hemolysin of streptococcus pyogens. I. Increased sensitivity of the isolated frog's heart to repeated application of the toxin. *J. Exper. Med.*, 81: 295, 1945.
11. Todd, E. W. Leukocidin of group A streptococci. *Brit. J. Exper. Path.*, 23: 136, 1942.
12. Todd, E. W., Laurent, L. J. M. and Hill, N. G. An examination of the relationship between streptococcal antitoxin and antistreptolysin. *J. Path. & Bact.*, 36: 201, 1933.
13. Todd, E. W. Antihaemolysin titers in haemolytic streptococcal infections and their significance in rheumatic fever. *Brit. J. Exper. Path.*, 13: 248, 1932.
14. Myers, W. K. and Keefer, C. S. Antistreptolysin content of the blood serum in rheumatic fever and rheumatoid arthritis. *J. Clin. Investigation*, 13: 155, 1934.
15. Lippard, V. W. and Johnson, P. Beta hemolytic streptococcic infection in infancy and in childhood. I. Antifibrinolysin and antistreptolysin response. *Am. J. Dis. Child.*, 49: 1411, 1935.
16. Stuart, R. D. Antistreptolysin titers of human sera in health and in various streptococcal infections. *J. Hyg.*, 36: 26, 1936.
17. Spink, W. W. and Keefer, C. S. Studies of hemolytic streptococcus infection. II. The serological reactions of the blood during erysipelas. *J. Clin. Investigation*, 15: 21, 1936.
18. Dawson, M. H. and Olmstead, M. Antistreptolysin titers in rheumatoid arthritis. *Proc. Soc. Exper. Biol. & Med.*, 34: 82, 1936.
19. Longcope, W. T. Studies of the variations in antistreptolysin titer of blood serum from patients with hemorrhagic nephritis. II. Observations on patients suffering from streptococcal infections, rheumatic fever and acute and chronic hemorrhagic nephritis. *J. Clin. Investigation*, 15: 277, 1936.
20. Lyttle, J. D., Seegal, D., Loeb, E. N. and Jost, E. L. The serum antistreptolysin titer in acute glomerulonephritis. *J. Clin. Investigation*, 17: 631, 1938.
21. Bunim, J. J. and McEwen, C. The antistreptolysin titer in rheumatic fever, arthritis, and other diseases. *J. Clin. Investigation*, 19: 75, 1940.
22. Earle, D. P., Jr., Seegal, D., Lyttle, J. D., Loeb, E. N. and Jost, E. L. The relation of serum antistreptolysin titer to exacerbation in chronic glomerulonephritis. *J. Clin. Investigation*, 21: 491, 1942.
23. Coburn, A. F. and Pauli, R. H. Studies on the immune response of the rheumatic subject and its relationship to activity of the rheumatic process. VI. The significance of the rise of antistreptolysin level in the development of rheumatic activity. *J. Clin. Investigation*, 14: 769, 1935.
24. Coburn, A. F. Observations on the mechanism of rheumatic fever. *Lancet*, 2: 1025, 1936.
25. Coburn, A. F. and Pauli, R. H. Significance of prolonged streptococcal antibody development in rheumatic fever. *J. Clin. Investigation*, 18: 141, 1939.
26. Mote, J. R. and Jones, T. D. Studies of hemolytic streptococcal antibodies in control groups, rheumatic fever and rheumatoid arthritis. I. The incidence of antistreptolysin "O," antifibrinolysin and hemolytic streptococcal precipitating antibodies in sera of urban control groups. *J. Immunol.*, 41: 35, 1941. II. The frequency of antistreptolysin "O," antifibrinolysin and precipitating-antibody responses in scarlet fever, hemolytic streptococcal infections and rheumatic fever. *J. Immunol.*, 41: 61, 1941. III. The magnitude of antistreptolysin "O," antifibrinolysin and precipitating-antibody responses; persistence of antibodies, and variations in antistreptolysin "O" curves in scarlet fever, hemolytic streptococcal infections and rheumatic fever. *J. Immunol.*, 41: 87, 1941.
27. Winblad, S. Studies in haemolytic streptococcus fibrinolysin, antifibrinolysin and antistreptolysin, with particular reference to rheumatic fever. *Acta path. et microbiol. Scandinav.*, 44: 1–229, 1941.
28. Taran, L. M., Jablon, J. M. and Weyr, Helen N. Immunologic studies in rheumatic fever. II. Antistreptolysin patterns in rheumatic children. *J. Immunol.*, 53: 381, 1946.
29. Green, C. A. Observations on the antistreptolysin O titer in relation to the mechanism of acute rheumatic fever. *J. Path. & Bact.*, 53: 223, 1941.
30. Rantz, L. A., Boisvert, P. J. and Spink, W. W. Hemolytic streptococcic and nonstreptococcic disease of the respiratory tract. A comparative clinical study. *Arch. Int. Med.*, 78: 369, 1946.
31. Rantz, L. A., Boisvert, P. J. and Clark, W. H. The relationship of serological types of group A hemolytic streptococci to toxin formation and antibody response. *Stanford M. Bull.* 6: 55, 1948.
32. Rantz, L. A. Boisvert, P. J. and Spink, W. W. The etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.*, 76: 131, 1945.
33. Rantz, L. A., Spink, W. W. and Boisvert, P. J. Hemolytic streptococcic sore throat: the course of the acute disease. *Arch. Int. Med.*, 79: 272, 1947.
34. Rantz, L. A., Boisvert, P. J. and Spink, W. W. Hemolytic streptococcus sore throat: the post-streptococcic state. *Arch. Int. Med.*, 79: 401, 1947.
35. Rantz, L. A. and Randall, E. A modification of the technique for the determination of the anti-

streptolysin titer. *Proc. Soc. Exper. Biol. & Med.*, 59: 22, 1945.

36. Dole, V. P., Watson, R. F. and Rothbard, S. Electrophoretic changes in the serum protein patterns of patients with scarlet fever and rheumatic fever. *J. Clin. Investigation*, 24: 644, 1945.
37. Lippard, V. W. and Wheeler, G. W. Beta hemolytic streptococcic infection in infancy and in childhood. III. Placental transmission of antifibrinolysin and antistreptolysin. *Am. J. Dis. Child.*, 52: 61, 1936.
38. Wilson, M. G., Wheeler, G. M. and Leask, M. M. Antistreptolysin content of blood serum of children. Its significance in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 31: 1001, 1934.
39. Rantz, L. A. and Randall, E. Unpublished observations.
40. Earle, D. P., Loeb, E. N., Seegal, D., Lyttle, J. D. and Jost, E. L. The serum antistreptolysin titer in chronic glomerulonephritis. *J. Clin. Investigation*, 21: 483, 1942.
41. Rantz, L. A., Rytand, D. A. and Randall, E. Unpublished observations.
42. Gordon, J. E. and Janney, J. H. Antistreptolysin content of the sera of normal infants and children. *J. Pediat.*, 18: 587, 1941.
43. Coburn, A. F. and Pauli, R. H. Limited observations on the antistreptolysin titer in relation to latitude. *J. Immunol.*, 29: 515, 1935.
44. Lemon, H. M. and Hamburger, M. Missed cases and contact carriers among nasal carriers of Beta hemolytic streptococci. *J. Immunol.*, 54: 189, 1946.
45. Spink, W. W., Rantz, L. A., Boisvert, P. J. and Coggeshall, H. An evaluation of sulfadiazine and penicillin in the therapy of patients with acute upper respiratory infections due to hemolytic streptococci, including tonsillitis, nasopharyngitis, and scarlet fever. *Arch. Int. Med.*, 77: 260, 1946.
46. Rantz, L. A., Boisvert, P. J. and Spink, W. W. Hemolytic streptococcal sore throat. Antibody response following treatment with penicillin, sulfadiazine and salicylates. *Science*, 103: 352, 1946.
47. Rantz, L. A. Group A hemolytic streptococcus antibodies. III. A study of the simultaneous infection of a large number of men by a single type. *Arch. Int. Med.*, 73: 238, 1944.
48. Rammelkamp, C. Personal communication.
49. Commission on Acute Respiratory Diseases. A study of food-borne epidemic of tonsillitis and pharyngitis due to beta hemolytic streptococcus, type 5. *Bull. Johns Hopkins Hosp.*, 77: 143, 1945.
50. Rantz, L. A. Antibacterial precipitating antibodies in group A hemolytic streptococcus sore throat. *Am. J. Med.*, 2: 55, 1947.

Streptococcal Fibrinolysin (Streptokinase)*

A Study of This Substance and Its Antibody in Group A Hemolytic Streptococcus Sore Throat†

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TILLET and Garner in 1933 described a substance formed by hemolytic streptococci which was able to induce the liquefaction of human plasma clots *in vitro*. It has usually been designated as streptococcal fibrinolysin.[1]‡ More recent investigation has demonstrated that this product of streptococcus is not a true lytic substance but is an enzyme activator or kinase, which activates the precursor of a protease which is present in normal human plasma.[2–5] The active enzyme will liquefy not only fibrin but other proteins as well. The suggestion has been made that the term "streptococcal fibrinolysin" be abandoned and that this substance be known as streptokinase.[6]

Large amounts of an antiprotease may appear or be present in plasma.[7] Fibrinolysin will not induce plasma clot lysis under these circumstances. This situation is observed most frequently in the presence of certain acute infections in man and in animal plasma.

Earlier work revealed that an antibody appeared during convalescence from hemolytic streptococcal infections which was able to inhibit the clot liquefying properties of fibrinolysin. This immune substance was absent in nearly all healthy human beings and present in many persons suffering from acute rheumatic fever[1,8,9,10] and hemorrhagic nephritis.

Recent studies have correlated the production of fibrinolysin with the serologic groups and types of hemolytic streptococcus and it has been demonstrated that an immunologically similar factor is formed members of groups A, C and G.[11,12] Strains of group A of various types, epidemic within the armed forces during the recent war, varied strikingly in their ability to make fibrinolysin *in vitro* and to stimulate the production of neutralizing antibody in infected human beings.[13,14]

Methods for the measurement of antifibrinolysin, based upon the time required for a broth culture of a standard strain of hemolytic streptococcus to induce lysis of the plasma clot of the individual under study, are relatively crude and do not express the concentration of antibody in quantitative terms.[1,15] A more precise method has been described recently.[16]

This paper is a report of a detailed study of a large number of cases of group A hemolytic streptococcus sore throat in military personnel. Serial measurements of the antifibrinolysin titer were made and the ability of the infecting streptococcus to form fibrinolysin *in vitro* was determined. The results were correlated with the natural history of the clinical disease.

‡ The information available on this subject in 1938 has been reviewed in detail.[1] No specific reference to the literature before that date will be made in this paper.

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CLINICAL MATERIAL

This report is based principally on a detailed study of 335 cases of group A hemolytic streptococcus sore throat in male military personnel who were admitted to a large station hospital. Patients were selected for inclusion in the study group on the basis of clinical and bacteriologic criteria that have been presented in great detail elsewhere.[17] Infection by group A hemolytic streptococci was established in 303 cases by the application of several immunologic procedures which were described in another report.[18] Serial antibody determinations were available in 243 of these during the fourth week after the onset of the acute respiratory infection. Most of the analyses in this paper will be based upon data collected from these 243 examples of proved streptococcal disease. Complete descriptions of the nature of the respiratory infections and of the suppurative and non-suppurative complications that frequently followed have been presented in a series of papers.[19–23]

METHODS

Plasma for antibody determinations was aseptically collected routinely on the second hospital day, again between the eighth and tenth and between the twenty-first to twenty-eighth days of illness, and at weekly intervals thereafter in certain cases. The antifibrinolysin concentration of plasma was determined by the method of Tillet and Garner[1] as modified by Boisvert.[10] A prolongation of clot lysis time of eight or more hours has been used as a measure of significant antibody response for the purpose of this study.

The *in vitro* production of fibrinolysin by group A hemolytic streptococci isolated from the respiratory passages of these patients was determined and recorded as follows: Streptococci were grown in neopeptone veal infusion broth for eighteen hours at 37°C. One-half ml. of the resultant culture, including the streptococcal cells, was added to .2 ml. of a standard* plasma and .8 ml. of normal saline. The mixture was clotted with .25 ml. of .25 per cent solution of calcium chloride. The time required for complete clot lysis was determined by frequent observation during incubation of the preparations in a water bath at 37°C. A number was assigned to each result as follows:

Plasma Clot Lysis Time	No. in Vitro
0 to 30 minutes	6
30 to 60 minutes	5
1 to 3 hours	4
3 to 8 hours	3
8 to 24 hours	2
No lysis in 24 hours	1

The mean of the *in vitro* numbers for all of the studied strains of hemolytic streptococci obtained from any individual patient has been used as a measure of the ability of the infectious agent in that patient to produce fibrinolysin *in vitro*.

FIBRINOLYSIN PRODUCTION

One hundred ninety-six patients in whom evidence of infection by only a single type was discovered were segregated into various categories on the basis of clinical and clinicopathologic study, and the mean production of fibrinolysin *in vitro* by the etiologic agent in each was determined. No correlation was discovered between *in vitro* production of fibrinolysin by the infecting hemolytic streptococcus and the severity of the initial illness as indicated by the height or duration of fever, the total leukocyte count or the initial erythrocyte sedimentation rate. The data upon which this statement is based have not been presented.

Certain details of the relationship between *in vitro* production of fibrinolysin by the infecting streptococcus and the development of complications are presented in Table 1. It will be observed that suppurative and non-suppurative complications followed

* Plasma from three healthy persons was pooled. A clot prepared from this material was lysed in fifteen minutes or less by cultures of strains of streptococci known to produce large amounts of fibrinolysin.

disease caused by organisms of every degree of lytic potency and that the mean production of lytic substance in uncomplicated cases and in every type of complication was comparable.

protein. Available evidence does not permit a decision as to whether very large amounts of the antibody, antifibrinolysin, or antiprotease have been concentrated in this fraction.

TABLE I

RELATIONSHIP BETWEEN THE *in vitro* PRODUCTION OF FIBRINOLYSIN BY THE INFECTING HEMOLYTIC STREPTOCOCCUS AND THE DEVELOPMENT OF SUPPURATIVE AND NON-SUPPURATIVE COMPLICATIONS

In vitro Fibrinolysin Production. No. of Infecting Streptococcus	Uncomplicated	Suppurative Complications	Non-suppurative Complications				
			All	Arthritis	Carditis	Late Fever	Other
1	11	2	3	1	0	1	1
2	10	2	4	1	0	0	3
3	25	0	6	3	0	2	1
4	31	3	4	2	1	1	0
5	21	3	5	0	1	1	3
6	44	6	13	4	1	3	5
Total	142	16	35	11	3	8	13
Mean *in vitro* number	4.2	4.3	4.2	4.0	5.0	4.2	4.2

ANTIFIBRINOLYSIN

The Antibody. Relatively little information is available in regard to the properties of antifibrinolysin since technics for its quantitation have not been satisfactory and because antiprotease, rather than antibody, has frequently been detected by the methods used.

The apparent distribution of this substance among the several plasma fractions of Cohn from a single pool of plasma is shown in Table II. The antibody was

TABLE II

	II	III-2	IV-1	IV-3-4	IV-6	IV-7	V
Concentration of gamma globulin (per cent)	95	27	1	0	0	5.5	0
Concentration of antifibrinolysin in units (Kaplan) per Gm. of dry protein	26,500	30	0	0	0	30	0

measured by the method described by Kaplan.[16] An antifibrinolytic substance was discovered only in fractions containing gamma globulin and was present in very large amounts in fraction II, which was composed almost entirely of this type of

Relationship of Initial Antifibrinolysin Titer to Nature of Clinical Disease. The antifibrinolysin titer of the serum at the onset of acute group A hemolytic streptococcus sore throat as expressed in clot lysis time in hours was compared with various features of the clinical disease. The concentration of antibody of 88 per cent of cases was very low (lysis time of three hours or less). (Table III.) In others the antiprotease of acute febrile illness interfered with the test. For these reasons this phase of the analysis was unsatisfactory and most of the data have not been presented. There was no relationship between the initial antifibrinolysin titer and the subsequent development of suppurative and non-suppurative complications. (Table III.)

Antibody Mechanics. The essential data derived from the study of the antifibrinolysin response in 243 cases of proved group A hemolytic streptococcus sore throat have been summarized in Table IV. Antibody levels at the onset of infection and those obtained eight to ten and twenty-one to twenty-eight days later are recorded. Therapeutic regimens, including the administra-

tion of penicillin, sulfadiazine and sodium salicylate in various amounts and combinations, were instituted in many of these patients. These procedures have been ignored throughout this paper since previous analyses indicated that none greatly altered in only twenty-eight, or 11.4 per cent, of all cases at this time. In ten of these, or 4.1 per cent of the whole group, clot lysis resistance was decreased by the eighth to tenth day, indicating that antiprotease, rather than antibody, was being detected.

TABLE III

RELATIONSHIP BETWEEN INITIAL ANTIFIBRINOLYSIN TITER AND THE DEVELOPMENT OF SUPPURATIVE AND NON-SUPPURATIVE COMPLICATIONS

Initial Plasma Clot Lysis Time (in hr.)	Uncomplicated		Suppurative Complications		Non-suppurative Complications					
					All		Arthritis	Carditis	Late Fever	Other
	No.	Per Cent	No.	Per Cent	No.	Per Cent				
0 to 1	133	82.1	24	92.3	45	81.8	15	4	11	15
1 to 3	10	6.2	0	0.0	3	5.4	1	0	0	2
3 to 8	3	1.8	0	0.0	1	1.8	0	1	0	0
8 to 24	2	1.2	1	3.8	2	3.6	0	0	1	1
24	14	8.6	1	3.8	4	7.3	0	2	0	2

TABLE IV

ANTIFIBRINOLYSIN RESPONSE IN 213 CASES OF GROUP A HEMOLYTIC STREPTOCOCCUS SORE THROAT

Initial Plasma Clot Lysis Time (in hr.)	Total Cases		Cases Unchanged Throughout*		Cases with Increase or Decrease in Clot Lysis Time of Any Magnitude										
					Observations at 8 to 10 Days						Observations during 4th Week				
					Cases Not Studied (days)	Clot Lysis Time (in hr.)					Clot Lysis Time (in hr.)				
	No.	Per Cent	No.	%†	8–10	0–1	1–3	3–8	8–24	24+	0–1	1–3	3–8	8–24	24+
0 to 1	202	83.1	103	50.9	6	56	6	3	6	22	1	21	11	8	58
1 to 3	13	5.3	1	7.7	2	2	1	1	1	5	0	1	1	4	6
3 to 8	4	1.6	0	0.0	1	0	2	0	1	0	0	0	1	1	2
8 to 24	5	2.0	0	0.0	2	0	0	1	1	1	0	1	0	1	3
24+	19	7.8	10	52.6	0	3	0	1	3	2	2	1	2	1	3

* No change in clot lysis time during four weeks of observation.

† Per cent of cases of this initial antibody level.

the natural history of the disease or the antibody response that accompanied it.[20,24]

Inspection of the table reveals that the initial plasma of 88.4 per cent of all cases contained only minimal amounts of antibody (clot lysis time of three hours or less). Increased resistance to clot lysis was present

A definite increase in antibody concentration had occurred by the eighth to tenth day in thirty-four, or 15.8 per cent, of 215 cases in which the initial antifibrinolysin level was low. During the fourth week a significant response was discovered in approximately 35 per cent of these patients.

An increase of clot resistance to lysis of a degree not believed to be significant was noted at this time in thirty-four additional cases. No alteration whatever in the lysis time was observed in 104 patients.

Certain of the other patients in whom increased amounts of antibody or antiprotease were present initially (clot lysis time of three or more hours) also exhibited a response. The number of such cases was small and interpretation of the results difficult. They will not be discussed in detail.

Serial antifibrinolysin determinations were available after the fourth week in a few cases, most of which were examples of non-suppurative poststreptococcal complications. Not one of the fifteen patients in whom maximal resistance to clot lysis was present during the fourth week exhibited a decrease in antibody concentration by the fortieth day after the onset of acute streptococcal respiratory infection. Occasional significant decrements in antibody level were observed at irregular intervals in the smaller group followed through the twelfth week. At this time clot lysis occurred in less than three hours in approximately 40 per cent of these patients.

Comment. The concentration of serum antifibrinolysin was very low in 90 per cent of young men at the onset of group A hemolytic streptococcus sore throat. Evidence of antiprotease activity was demonstrated at this time in a very few cases. A significant antibody response occurred in approximately 16 per cent of cases by the eighth to tenth days, and an additional 19 per cent by the fourth week of illness. Significant decrements in antibody concentration were first observed after the sixth week and had been detected in 40 per cent of a very small group followed through the twelfth week.

TABLE V

RELATIONSHIP OF HEIGHT AND DURATION OF FEVER TO FREQUENCY OF SIGNIFICANT ANTIFIBRINOLYSIN RESPONSE

	Maximum Temperature—°F.					Duration of Fever in Days				
	98.6 to 99.9	100.0 to 100.9	101.0 to 101.9	101.0 to 102.9	103+	0–1	2	3	4	5 or more
Number of cases	16	20	49	54	104	45	60	67	37	34
Number of significant antifibrinolysin responses	2	5	14	19	38	11	15	22	15	15
Percentage of significant antifibrinolysin responses	12.5	25.0	28.6	35.2	36.5	24.4	25.0	32.8	40.5	44.1

RELATIONSHIP OF FREQUENCY OF ANTIFIBRINOLYSIN RESPONSE TO NATURE OF CLINICAL DISEASE

The data obtained from a study of 243 of 303 proved cases of group A hemolytic streptococcus sore throat were an alyztoed determine the relationship between the frequency of antifibrinolysin response and the nature of the acute illness and complications which often followed it. Patients were selected for inclusion in the group only if follow-up antibody determinations were made during the fourth week after the onset of infection.

Acute Suppurative Disease. A definite relationship between certain manifestations of the acute suppurative phase of hemolytic streptococcus sore throat and the frequency of significant antifibrinolysin response has been demonstrated. Such an increase in antibody occurred more often as the maximum temperature became greater or more prolonged. (Table v.) The differences were most striking when height of fever was considered. No correlation between antibody response and initial leukocyte count or erythrocyte sedimentation rate was noted.

Suppurative Complications. The course of twenty-six of these cases of hemolytic streptococcus sore throat was complicated by the development of suppurative disorders. Peritonsillar abscess, otitis media and sinusitis were observed. The frequency of significant antifibrinolysin response was greater in these patients (46.1 per cent) than in uncomplicated cases (25.3 per cent) and the difference is of statistical significance.

TABLE VI

RELATIONSHIP OF THE PRESENCE OF SUPPURATIVE AND NON-SUPPURATIVE COMPLICATIONS TO THE FREQUENCY OF SIGNIFICANT ANTIFIBRINOLYSIN RESPONSE

	Type of Case						
	Uncomplicated	Suppurative Complications	Non-suppurative Complications				
			All	Arthritis	Late Fever	Carditis	Other
Number of cases	162	26	55	16	12	7	20
Number of cases with plasma clot lysis time of less than 60 minutes throughout illness	64	8	11	4	2	3	2
Number of significant antifibrinolysin responses	41	12	25	7	7	1	10
Percentage of significant antifibrinolysin responses	25.3	46.1	45.5	43.7	53.3	14.3	50.0

Non-suppurative Complications. A considerable number of hemolytic streptococcus respiratory infections in this study group initiated pathologic processes, apparently of a non-suppurative nature. Clinical manifestations of these disorders were arthritis with or without fever or carditis (rheumatic fever), late fever with or without carditis and carditis without fever or arthritis. Twenty less clearly defined pathologic states are segregated in a separate category.

The data summarized in Table VI reveal that the frequency of significant antifibrinolysin response was greater in the presence of all forms of non-suppurative poststreptococcal disorders except carditis than in uncomplicated cases. These differences are of statistical significance when the values obtained for the total complicated group are compared with those for the uncomplicated subjects.

An increase in antifibrinolysin is not essential in the pathogenesis of the phenomena of the poststreptococcal state since these disorders appeared in many persons in whom increased resistance to clot lysis was at all times absent. (Table VI.) This important fact is further emphasized by the data presented in Table VII in which is summarized the results obtained when the antifibrinolysin content of sera obtained during the course of hemolytic streptococcus sore throat complicated by arthritis (rheumatic fever) was determined by the more precise Kaplan method.[16] An increase in antibody occurred in six of eight cases but was not of great magnitude in three in

TABLE VII

ANTIFIBRINOLYSIN RESPONSE IN EIGHT CASES OF POST-STREPTOCOCCAL ARTHRITIS IN WHICH THE ANTIBODY WAS STUDIED BY THE KAPLAN METHOD

	Case Number							
	1	2	3	4	5	6	7	8
Types of infecting streptococcus	19	19	26	36	36	36	36	46
Increase in serum antifibrinolysin in units per ml	575	11	483	58	47	0	0	1975
Increase in dilution tubes	6	1	2	3	2	0	0	8
Maximum serum antifibrinolysin titer in units per ml	625	36	900	83	83	<25	<25	2100

whom the peak antifibrinolysin titer was never greater than 58 units. Of greater interest were two subjects who developed arthritis in the absence of measurable (less than 25 units per ml.) serum antifibrinolysin at any time during the course of the illness.

Earlier in this section it was demonstrated that the frequency of the antifibrinolysin response was related to the severity of the initial suppurative phase of hemolytic streptococcus sore throat. It should be recalled at this time that evidence presented elsewhere[25] indicated that non-suppurative complications were more likely to follow severe than mild forms of this disease.

COMMENT

Group A hemolytic streptococci produce a substance, usually called fibrinolysin, which is able to activate a protease present in normal human plasma and thus to induce liquefaction of human plasma clots *in vitro*. Earlier investigators suggested that the invasiveness of these organisms might be enhanced by the elaboration of this substance *in vivo* with a dissolution of the fibrin deposits that normally participate in the localization of infections.[1] This hypothesis may be correct if infections other than those of the upper respiratory tract are considered.

The results of the present study showed that none of the clinical manifestations of acute group A hemolytic streptococcal sore throat could be related to the *in vitro* production of fibrinolysin by the infecting organism. Furthermore, disease of great severity and suppurative and non-suppurative complications were observed in patients whose infection was caused by strains (notably of type 3) the *in vitro* lytic activity of which was slight.

An antibody often appears in the serum of human beings during convalescence from hemolytic streptococcal infection that neutralizes the enzyme activating property of this bacterial product. Investigation of this immune substance has been hampered by the relatively crude methods available for its quantitative estimation. Recent studies have indicated that the frequency of significant antibody response in a group of unselected hemolytic streptococcal respiratory infections is largely dependent on the ability of the infectious agents to form fibrinolysin.

The data obtained from the study of a large number of cases of group A hemolytic streptococcus sore throat have been pooled and considered together in the present analysis of antibody response. The lytic and antibody stimulating properties of the isolated streptococci varied greatly with their serologic type. It was believed, however, that useful information might be obtained from this analysis since it has been shown in previous reports[17,20,21] that the natural history of the disease was not related to the serologic type of causative streptococcus (except for rash formation), and it has just been demonstrated that a similar situation prevails in regard to *in vitro* production of fibrinolysin.

An increment in antifibrinolysin of significant magnitude occurred in 16 per cent of all cases by the eighth to tenth day, and in an additional 19 per cent by the fourth week after the onset of acute streptococcal illness.

A more severe acute respiratory illness, as indicated by the height and duration of fever, was associated with a significantly greater frequency of antifibrinolysin response. Similarly, the incidence of antibody response was greater in the presence of suppurative and non-suppurative complications than in uncomplicated cases. A similar observation was made by certain earlier investigators.[1] In an extensive study Mote and Jones also demonstrated a greater frequency of antifibrinolysin response when hemolytic streptococcal infection was followed by the development of arthritis than when it was not. The differences described were not great.[8]

In two previous reports[25,26] it has been noted that an antibacterial precipitating antibody appeared or was present initially more often in the serum of persons whose

acute streptococcal illness was followed by the development of arthritis and that the magnitude of the increase in antistreptolysin "O" was greater in association with all forms of non-suppurative poststreptococcal disorders. These pathologic states may be the result of hypersensitivity of the anaphylactic type and it was suggested that the presence of abnormal concentrations of these antibodies might be directly responsible for an increased tissue sensitivity in patients in whom such complications develop. Under these circumstances the X-antigen or streptolysin "O" could be regarded as the sensitizing substance *per se*.

On the other hand, it was proposed that the increased production of antibodies by persons who had developed a poststreptococcal complication simply mirrored a generally increased immunologic hyperreactivity on the part of these patients which led to the development of sensitivity states in which the X-anti-X antibody or the streptolysin "O"-antistreptolysin "O" systems had no specific rôle. It was also emphasized that non-suppurative complications most often followed the more severe initial infections that were associated with an exaggerated antistreptolysin response, and also that these disorders appeared in certain patients in whom the serum concentrations of these antibodies was always low.

An analogous situation has now been demonstrated in regard to fibrinolysin and it becomes increasingly apparent that the excessive formation of antibodies by persons who develop the disorders of the poststreptococcal state is indeed the result of a non-specific immunologic hyperreactivity. This mechanism seems particularly applicable to the explanation of the augmented production of antistreptolysin and antifibrinolysin which has been described. It does not clearly elucidate the phenomena observed in relationship to the anti-X antibody since this substance was demonstrated in abnormal amounts only in the presence of arthritis and since joint disease appeared with unusual frequency in persons in whom the antibody was present at the onset of acute respiratory infection as well as in those in whom it appeared later.

Further speculation as to the rôle of these several antigen-antibody systems in the pathogenesis of the poststreptococcal and non-suppurative disorders cannot be profitable. The great importance of these serious pathologic states demands that all of these phenomena be further investigated and the effect of the injection of various antigens in purified form in human beings determined.

SUMMARY

1. A large number of group A hemolytic streptococcal respiratory infections in young men have been studied.

2. No relationship was discovered between any clinical feature of the disease or its complications and the ability of the infecting hemolytic streptococcus to form fibrinolysin *in vitro*.

3. The serum concentration of antifibrinolysin was low in 90 per cent of the subjects at the onset of their infection.

4. An increase in antibody of significant magnitude had occurred in 35 per cent of these patients by the fourth week after the onset of acute respiratory illness.

5. An antibody response occurred more frequently when the respiratory disease was severe or when a suppurative or nonsuppurative complication supervened.

REFERENCES

1. Tillett, W. S. The fibrinolytic activity of hemolytic streptococci. *Bact. Rev.*, 2: 161, 1938.
2. Milstone, H. A factor in normal human blood which participates in streptococcal fibrinolysis. *J. Immunol.*, 42: 109, 1942.
3. Kaplan, M. H. Nature and role of the lytic factor in hemolytic streptococcal fibrinolysis. *Proc. Soc. Exper. Biol. & Med.*, 57: 40, 1944.
4. Christensen, L. R. Streptococcal fibrinolysis. A proteolytic reaction due to a serum enzyme activated by streptococcal fibrinolysin. *J. Gen. Physiol.*, 28: 559, 1945.
5. Kaplan, M. H. Studies of streptococcal fibrinolysis. I. The dissimilarity of serum protease and trypsin as indicated by the separate specificities of their kinases, fibrinolysin, and enterokinase. *J. Clin. Investigation*, 25: 331, 1946.
6. Ferguson, J. H. Nomenclature of parenteral proteases. *Science*, 105: 488, 1947.

7. KAPLAN, M. H. Studies of streptococcal fibrinolysis. II. The inhibition of streptococcal fibrinolysis by antifibrinolysin and antiprotease. *J. Clin. Investigation*, 25: 337, 1946.
8. (*a*) MOTE, J. R. and JONES, T. D. Studies of hemolytic streptococcal antibodies in control groups, rheumatic fever and rheumatoid arthritis. I. The incidence of antistreptolysin "O," antifibrinolysin and hemolytic streptococcal precipitating antibodies in sera of urban control groups. *J. Immunol.*, 41: 35, 1941. (*b*) II. The frequency of antistreptolysin "O," antifibrinolysin and precipitating-antibody responses in scarlet fever, hemolytic streptococcal infections and rheumatic fever. *J. Immunol.* 41: 61, 1941. (*c*) III. The magnitude of antistreptolysin "O," antifibrinolysin and precipitating-antibody responses; persistence of antibodies, and variations in antistreptolysin "O" curves in scarlet fever, hemolytic streptococcal infections and rheumatic fever. *J. Immunol.*, 41: 87, 1941.
9. WINBLAD, S. Studies in hemolytic streptococcus fibrinolysin, antifibrinolysin and antistreptolysin, with particular reference to rheumatic fever. *Acta path. et microbiol. Scandinav.*, 44: 1–229, 1941.
10. BOISVERT, P. J. The streptococcal antifibrinolysin test in clinical use. *J. Clin. Investigation*, 19: 65, 1940.
11. LANCEFIELD, R. C. Specific relationship of cell composition to biological activity of hemolytic streptococci. In Harvy Lectures, 1940–1941. Baltimore, 1941. Williams & Wilkins Co.
12. KAPLAN, M. H. and The Commission on Acute Respiratory Diseases. Immunological similarity of streptococcal antifibrinolysins. *Proc. Soc. Exper. Biol. & Med.*, 63: 50, 1946.
13. RANTZ, L. A., SPINK, W. W. and BOISVERT, P. J. The relationship of serologic types of group A hemolytic streptococci to toxin formation and antibody response. *J. Clin. Investigation*, 25: 911, 1946.
14. KAPLAN, M. H. and The Commission on Acute Respiratory Diseases. A quantitative study of the fibrinolysin-antifibrinolysin reaction. *Science*, 101: 120, 1945.
15. (*a*) MASSELL, B. F., MOTE, J. R. and JONES, T. D. The quantitative relation of fibrinolysin and antifibrinolysin. *J. Immunol.*, 36: 45, 1939. (*b*) MOTE, J. R., MASSELL, B. F. and JONES, T. D. The factors effecting quantitative relation of fibrinolysin and antifibrinolysin. *J. Immunol.*, 36: 59, 1939.
16. (*a*) KAPLAN, M. H. In collaboration with The Commission on Acute Respiratory Diseases. Studies of streptococcal fibrinolysis. III. A quantitative method for the estimation of serum antifibrinolysin. *J. Clin. Investigation*, 25: 347, 1946. (*b*) COMMISSION ON ACUTE RESPIRATORY DISEASES. IV. Clinical application of a quantitative antifibrinolysin test. *J. Clin. Investigation*, 25: 352, 1946.
17. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. Hemolytic streptococcic and nonstreptococcic disease of the respiratory tract. A comparative clinical study. *Arch. Int. Med.*, 78: 369, 1946.
18. RANTZ, L. A., BOISVERT, P. J. and CLARK, W. H. The relationship of serological types of Group A hemolytic streptococci to toxin formation and antibody response. *J. Clin. Investigation*, (in press).
19. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. Etiology and pathogenesis of rheumatic fever. *Arch. Int. Med.*, 76: 131, 1945.
20. RANTZ, L. A., SPINK, W. W. and BOISVERT, P. J. Hemolytic streptococcic sore throat. The course of the acute disease. *Arch. Int. Med.*, 79: 272, 1947.
21. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. Hemolytic streptococcus sore throat. The post-streptococcic state. *Arch. Int. Med.*, 79: 401, 1947.
22. RANTZ, L. A., SPINK, W. W. and BOISVERT, P. J. Abnormalities in the electrocardiogram following hemolytic streptococcus sore throat. *Arch. Int. Med.*, 77: 66, 1946.
23. RANTZ, L. A. The natural history of hemolytic streptococcus sore throat. *California & West. Med.*, 65: 266, 1946.
24. RANTZ, L. A., BOISVERT, P. J. and SPINK, W. W. Hemolytic streptococcal sore throat. Antibody response following treatment with penicillin, sulfadiazine and salicylates. *Science*, 103: 352, 1946.
25. RANTZ, L. A., RANDALL, E. and RANTZ, H. H. Antistreptolysin "O." A study of this antibody in health and in hemolytic streptococcus respiratory disease in man. *Am. J. Med.*, 5: 3, 1948.
26. RANTZ, L. A. and RANDALL, E. Antibacterial precipitating antibodies in group A hemolytic streptococcus sore throat. *Am. J. Med.*, 2: 551, 1947.

Immediate Pressor Effect of Desoxycorticosterone Acetate in Arterial Hypertension*

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REPEATED intramuscular injections of desoxycorticosterone acetate (DCA) and sodium chloride have been reported to produce renal vascular lesions in rats,[1] to elevate the blood pressure of patients with arterial hypertension[2,3] and to elevate the blood pressure above normal in patients with Addison's disease when they are given in sufficient amounts.[4] The blood pressure of normal individuals has also been raised by intramuscular injections of DCA but only after more prolonged treatment.[5] The present report deals with the effect of intravenous injections of DCA and other related hormones upon the blood pressure of both normotensive and hypertensive human subjects.

METHODS

A Hamilton optical manometer was used to record direct arterial pressure before, during and after the injection of test substances.[6] The ear and finger pulses were recorded in thirty-two instances by photoelectric plethysmography. The electrocardiogram (lead II) was taken after two injections of DCA. The cardiac output was estimated by the ballistocardiograph in seven instances. The venous pressure was measured by an optical manometer in six instances and the skin temperature was followed in three instances by copper-constantan thermocouples. (Figs. 1 and 2.)

The recipients of the various injections were eleven hypertensive subjects, five normotensive subjects and four exhibiting coarctation of the aorta with normal diastolic pressures. The various substances tested intravenously were DCA, progesterone, Δ^5 pregnenolone, testosterone, dehydroisoandrosterone acetate and 17-hydroxy-11-dehydrocorticosterone. (Fig. 3.) As most of these compounds are quite insoluble in water, 5 mg. of each crystalline steroid compound was dissolved in 2.5 ml. of propylene glycol.[7,8] Sixteen experiments were controlled by the injection of 2.5 ml. of propylene glycol. In addition 10 ml. of adrenal cortical extract were injected into three hypertensive individuals, controlled by the injection of 10 ml. of 10 per cent alcohol. To facilitate dissolving the crystalline steroids in propylene glycol the solutions were warmed over a steam bath for several minutes. An attempt was made to dissolve desoxycorticosterone, but it was found to be only slightly soluble in propylene glycol and therefore was not used in the present experiments.

In four experiments the response of the blood pressure to a single intramuscular injection of 10 mg. of DCA in peanut oil was followed for several days by the auscultatory method. Similarly, the response to 5 mg. of DCA given intravenously was followed in seven instances. All patients given DCA received 5 to 8 Gm. of sodium chloride in their diets, except one (T. A.) who received 2 Gm. for eight days prior to the experiment.

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RESULTS

A significant, slowly developing rise in blood pressure (16 to 33 mm. Hg diastolic) followed the intravenous injection of DCA in hypertensive subjects. (Table I.) This rise became apparent about ten minutes after the injection and lasted from one-half to forty-eight hours. Other steroids used as controls, namely, progesterone, Δ^5 pregnenolone, testosterone, dehydroisoandrosterone acetate, adrenal cortical extract and 17-hydroxy-11-dehydrocorticosterone did not show significant pressor effects when injected into hypertensive subjects. (Table I.) Since these compounds were inactive on blood pressure in hypertensives, they were not used in normotensive individuals. In no case did DCA cause a significant elevation of the diastolic pressure of normotensive subjects. These included four patients with

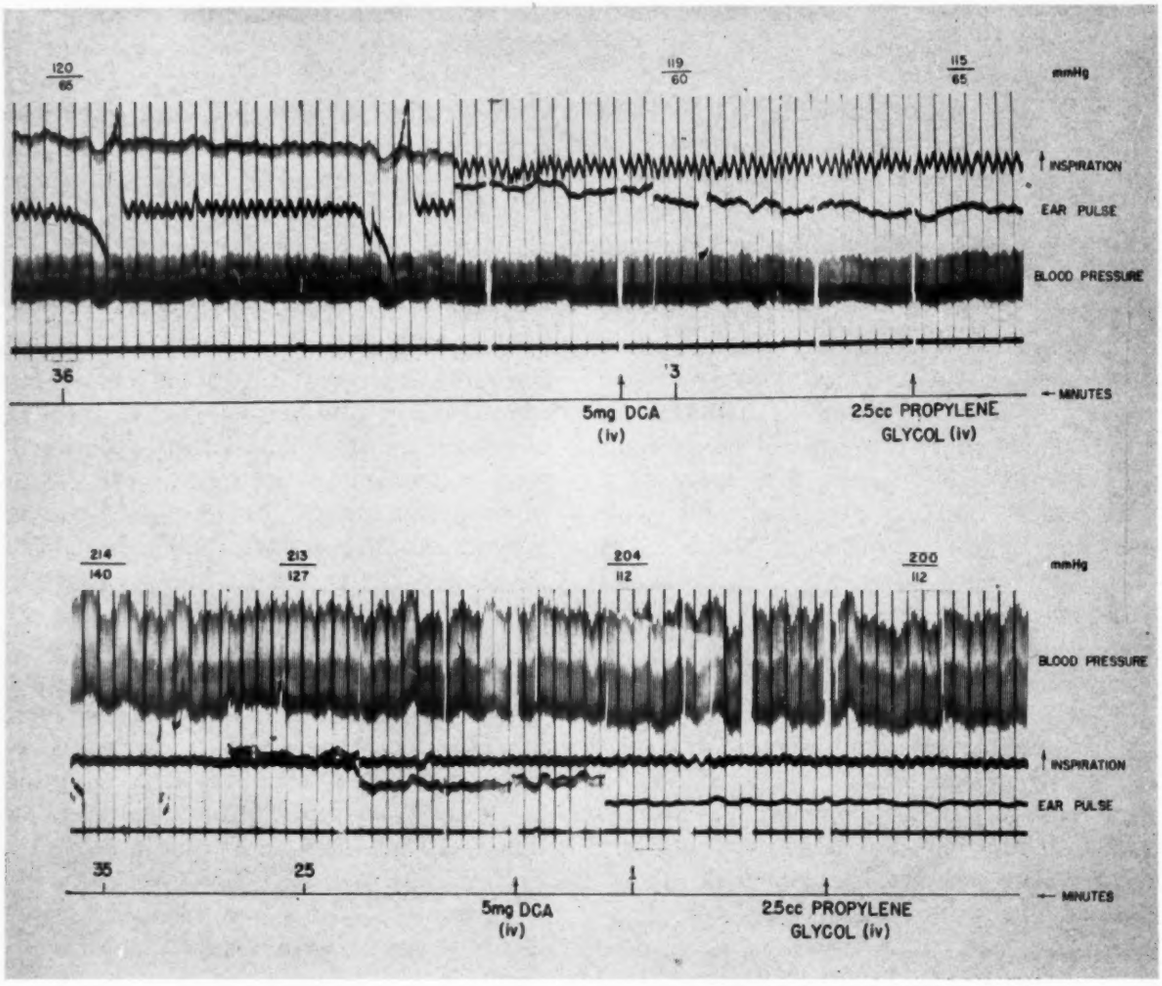

FIG. 1. The effects on blood pressure, ear pulse and respiration of the intravenous injection of propylene glycol and of DCA in propylene glycol in a normotensive (V.E.) (upper graph) and a hypertensive (I.H.) (lower graph). (Record reads from right to left.) Blood pressure values (in mm. Hg) are the average during one minute. Representative sections were taken from the original continuous records. The black vertical lines are at six-second intervals. The interruptions in the blood pressure record indicate duration of injections. The normotensive record shows the effect on blood pressure and ear pulse with voluntary deep inspiration and expiration. In the lower graph DCA was injected five minutes after propylene glycol. Note the gradual rise in diastolic pressure.

TABLE I

CHANGES IN BLOOD PRESSURE (MM. HG) AFTER AN INTRAVENOUS INJECTION OF 5 MG. OF DESOXYCORTICOSTERONE ACETATE AND OTHER STEROIDS

Patient	Substance*	Controls				5 mg. DCA			
		Before	After	Maximum Change	Time of Change (min.)	Before	After	Maximum Change	Time of Change (min.)
Hypertensive									
F. W. ♀	P. G.	208/131	213/134	+ 5/+ 3	2	213/134	217/150	+ 4/+16	16
L. C. ♀	P. G.	237/110	232/127	− 5/+17†	35	232/127	280/160	+48/+33	10
I. H. ♀	P. G.	203/115	209/122	+ 6/+ 7	5	209/122	217/145	+ 8/+23	30
	Progesterone	191/105	203/115	+12/+10	10				
D. R. ♀	P. G.	216/120	226/130	+10/+10	6	229/135	240/150	+11/+15	17
	Progesterone	226/130	229/135	+ 3/+ 5	10				
B. C. ♂	P. G.	175/120	169/120	− 6/ 0	19	168/117	180/128	+12/+11	25
	Testosterone	169/120	168/117	+ 1/+ 3	22				
T. A. ♂	.....	.....	.....	.....	..	197/157	217/175	+20/+18	10
M. L. ♀	.....	.....	.....	.....	..	217/ 98	235/122	+18/+24	5
D. B. ♀	.....	.....	.....	.....	..	188/105	215/128	+27/+23	11
M. P. ♀	P. G.	183/101	211/119	+28/+18†	12				
	Δ^5 Pregnenolone	211/119	219/127	+ 8/+ 8	13				
	Dehydroisoandrosterone	219/127	214/121	− 5/− 6	25				
D. R. ♀	P. G.	215/128	231/137	+16/+ 9	5				
	Δ^5 Pregnenolone	231/137	236/147	+ 5/+10	26				
	Dehydroisoandrosterone	236/147	244/151	+ 8/+ 4	16				
F. W. ♀	Testosterone	194/115	210/125	+16/+10	20				
F. W. ♀	P. G.	185/110	200/118	+15/+ 8	16				
	Compound E	190/110	193/118	+ 3/+ 8	24				
D. B. ♀	Compound E	168/100	198/116	+30/+16	20				
D. B. ♀	Compound E	200/119	203/125	+ 3/+ 6	17				
W. D. ♂	10 ml. ethanol (10%)	214/123	214/127	0/+ 4	5				
	Adrenal cortical extract (10 ml.)	214/127	212/124	− 2/− 3	35				
F. W. ♀	10 ml. ethanol (10%)	194/106	208/113	+14/+ 7	4				
	Adrenal cortical extract (10 ml.)	208/113	199/115	− 9/+ 2	20				
W. D. ♂	Adrenal cortical extract (10 ml.)	201/115	195/117	− 6/+ 2	25				
Normotensive									
W. G. ♂	P. G.	122/ 64	130/ 66	+ 8/+ 2	6	130/ 66	133/ 66	+ 3/ 0	15
V. E. ♀	P. G.	114/ 56	119/ 60	+ 5/+ 4	3	119/ 60	120/ 64	+ 1/+ 4	34
J. M. ♂	P. G.	101/ 63	102/ 62	+ 1/− 1	1	102/ 62	107/ 66	+ 5/+ 4	14
C. C. ♀ ‡	P. G.	154/ 74	172/ 66	+18/− 8	30	196/ 65	179/ 63	−17/− 2	9
F. R. ♀ §	P. G.	145/ 61	147/ 65	+ 2/+ 4	34	147/ 65	155/ 70	+ 8/+ 5	14
A. D. ♂ §	P. G.	200/ 80	212/ 95	+12/+15	4	212/ 95	212/ 93	0/− 2	36
J. F. ♂ §	.....	.....	.....	.....	..	171/ 85	168/ 87	− 3/+ 2	42
L. H. ♂ §	.....	.....	.....	.....	..	194/ 98	195/108	+ 1/+10	17
L. H. ♀	.....	.....	.....	.....	..	120/ 60	132/ 61	+12/+ 1	27
E. W. ♂	P. G.	112/ 57	117/ 60	+ 5/+ 3	5	119/ 64	107/ 62	−12/− 2	34
	Progesterone	117/ 60	119/ 64	+ 2/+ 4	24				
M. P. ♀	P. G.	111/ 57	122/ 66	+11/+ 9	4	117/ 64	125/ 68	+ 8/+ 4	12
	Progesterone	122/ 66	117/ 64	− 5/− 2	23	117/ 64	120/ 61	+ 3/− 3	49

* P. G. = 2.5 ml. propylene glycol; 5 mg. progesterone, testosterone, Δ^5 pregnenolone, 17-hydroxy-11-dehydrocorticosterone (compound E), and dehydroisoandrosterone acetate dissolved in 2.5 ml. propylene glycol.

† Severe pain during injection.

‡ This patient exhibited a high systolic pressure of undetermined etiology.

§ Coarctation of aorta.

Blood pressures indicate the average systolic and diastolic values during one-half to one minute at the period of maximum change.

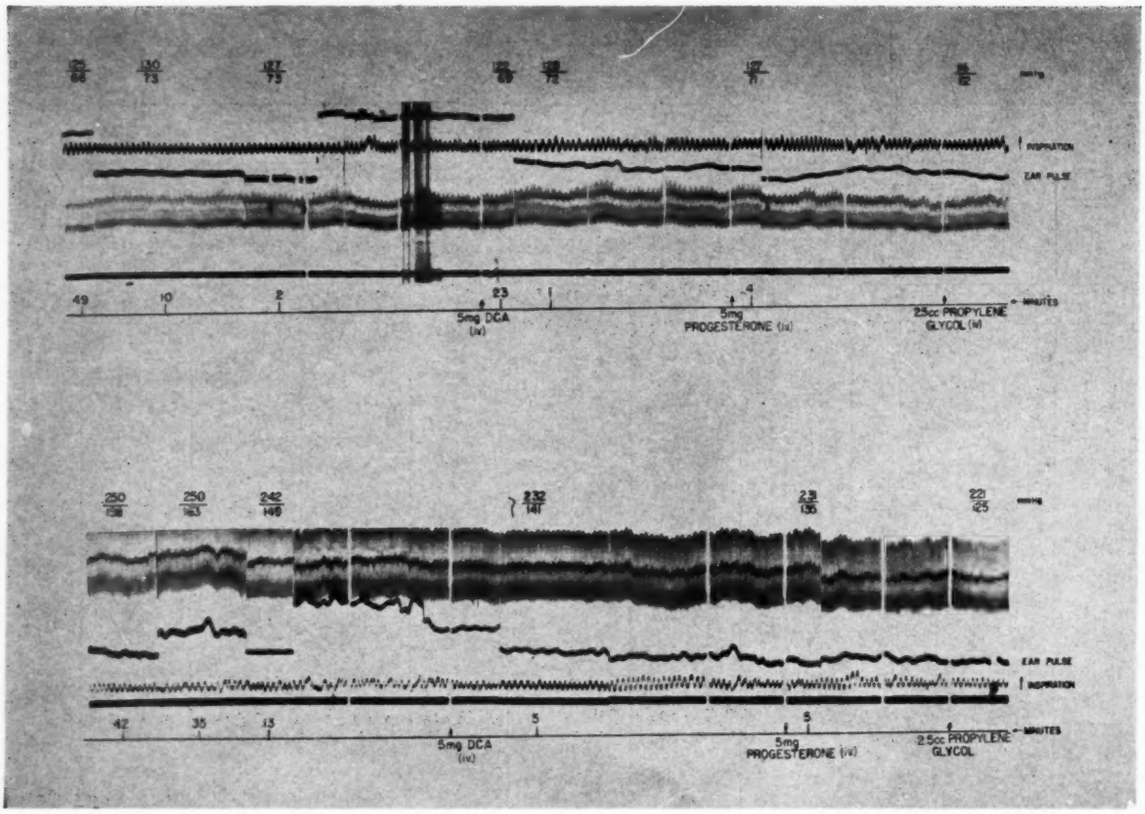

FIG. 2. The effects on blood pressure, ear pulse and respiration of the intravenous injection of propylene glycol, progesterone and DCA in a normotensive (M.P.) (upper graph) and a hypertensive (D.R.) (lower graph). (Notations same as Figure 1.) The black vertical line on the upper record indicates the end of the injection of DCA. The systolic pressures at thirteen, thirty-five and forty-two minutes of the lower record were obtained by calibration of the kymographic camera scale since the photographic paper was not wide enough to record these values. Note the very slight effect of progesterone as compared to DCA.

TABLE II

PROLONGED BLOOD PRESSURE RESPONSE TO INTRAMUSCULAR AND INTRAVENOUS INJECTIONS OF DCA IN HYPERTENSIVE PATIENTS (MM. HG)

	10 mg. DCA Intramuscularly				5 mg. DCA Intravenously			
	Average Blood Pressure Before	Average Blood Pressure After	Change	Days* After DCA	Average Blood Pressure Before	Average Blood Pressure After	Change	Days* After DCA
L. C. ♀	178/108	208/138	+30/+30	3	204/125	208/134	+4/+9	3
	193/118	204/126	+11/+8	3				
M. L. ♀	153/95	182/104	+29/+9	2	144/84	167/94	+23/+10	5
	150/90	175/117	+25/+27	6				
B. C ♂	.....	.....	.....	..	160/93	188/129	+28/+36	2
T. A. ♂	.....	.....	.....	..	208/160	201/158	−7/−2	1
I. H. ♀	.....	.....	.....	..	162/98	144/93	−18/−5	4†
D. R. ♀	.....	.....	.....	..	209/143	212/153	+3/+10	2
D. B. ♀	.....	.....	.....	..	154/109	172/116	+18/+7	2

* Blood pressure averages were taken for this period of time following the injection of DCA.

† Experiment done eleven days after 10 mg. DCA intramuscularly for seventeen days.

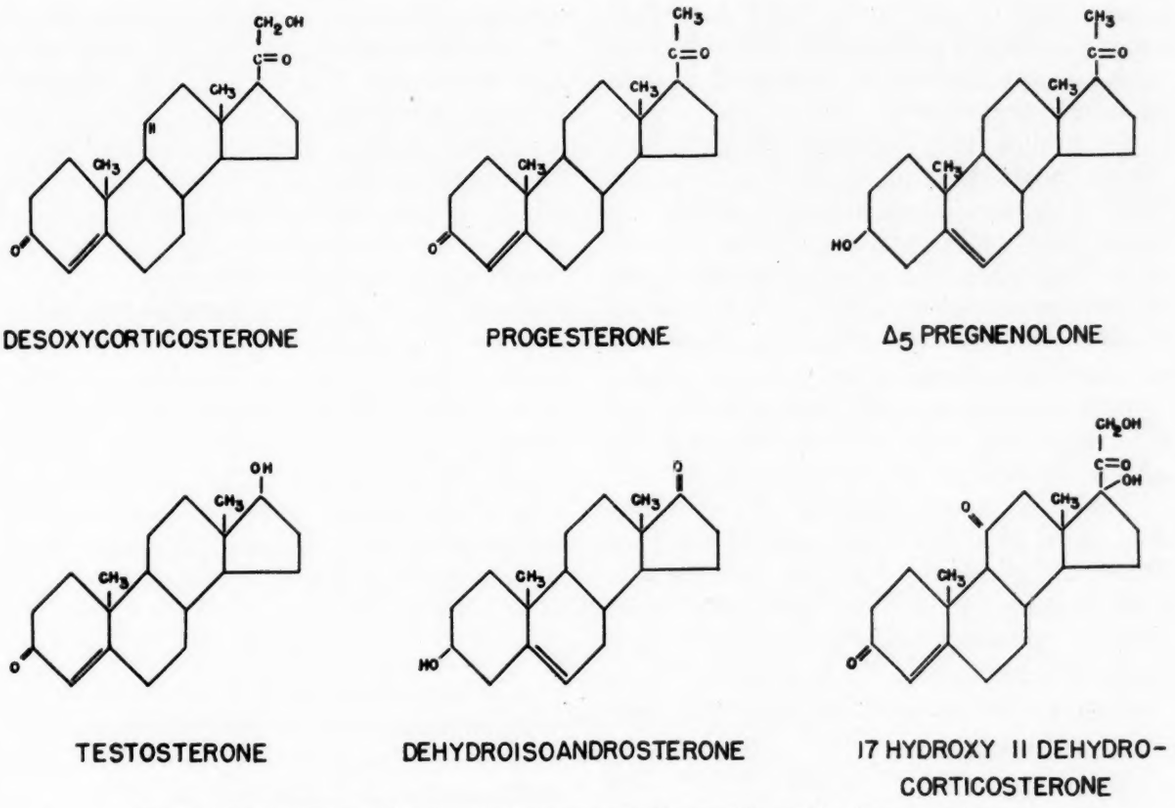

FIG. 3. The similarity of the chemical structures of the steroids used in these experiments.

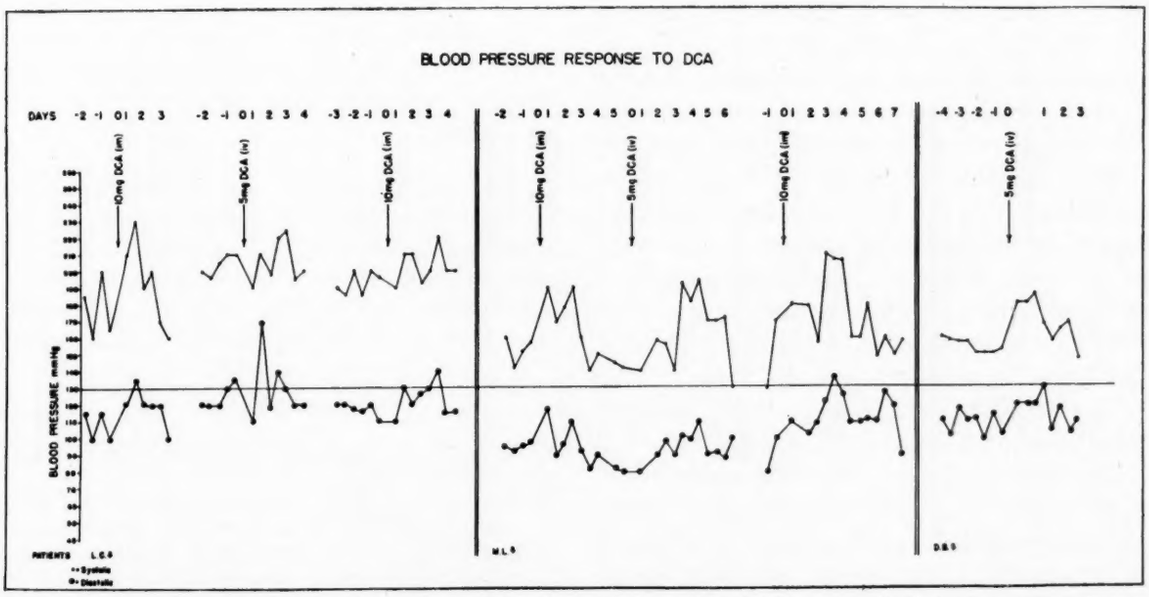

FIG. 4. Prolonged response of blood pressure in three hypertensive subjects following a single intravenous or intramuscular injection of DCA. Blood pressures were recorded twice daily (8:00 A.M. and 2:00 P.M.) after thirty minutes of bed rest by the auscultatory method. The upper level represents the systolic, the lower represents the diastolic pressure.

coarctation of the aorta who exhibited normal diastolic pressures in both brachial and femoral arteries as measured with a Hamilton manometer.

Sometimes the injection of propylene glycol caused pain along the course of the vein. This was immediately abolished by subsequent injection of normal saline solution. This pain was inconstant but when present appeared to affect blood pressure in two hypertensive individuals. There was no correlation between the presence of pain (which was momentarily severe during ten injections and slight during 12) and the eventual action of the compound injected.

Three of seven hypertensive patients responded to a single injection of 5 mg. of DCA intravenously or 10 mg. intramuscularly by a significant rise in both systolic and diastolic pressures for as long as forty-eight hours. (Table II, Fig. 4.) In addition, these patients complained of exacerbation or intensification of their clinical symptoms such as headache, nervousness and restlessness.

COMMENTS

From the results of these experiments a question arises as to the manner in which DCA affects the blood pressure. Judging from the ballistocardiographic studies, the cardiac output was not increased. Perera et al. have shown, when DCA is injected intramuscularly over several days, that the increase in blood pressure in hypertensive individuals cannot be correlated with abnormal retention of the sodium ion or with an increase in circulating blood volume.[3] The circulation in the ear lobe, fingers and toes did not decrease as would occur if there had been vasoconstriction in these areas. It is possible, therefore, that visceral vascular beds may have been affected.

The four subjects exhibiting coarctation of the aorta deserve comment. All of them showed normal diastolic pressures although their systolic levels were relatively high. Their failure to respond to the intravenous injection of DCA suggests that their systolic hypertension was not on the same basis as patients with diastolic hypertension. It will be necessary to compare these patients with others having coarctation and elevated diastolic pressures.

Three of seven patients appeared to be extremely sensitive to administration of DCA, responding by prolonged increases in the levels of blood pressure and by exacerbation of their symptoms. Whether these increases exhibit a different type of the disease in which the activity of the adrenals is relatively greater, as distinguished from the usual case of arterial hypertension, remains to be elucidated. At any rate, it it would seem that DCA, a compound chemically related to adrenal cortical hormones, acts as a pressor substance when hypertension is already established.

SUMMARY

1. Five mg. of DCA,* progesterone, Δ^5 pregnenolone, testosterone, dehydroisoandrosterone acetate, 17-hydroxy-11-dehydrocorticosterone† (dissolved in 2.5 cc. of propylene glycol) and 10 ml. of adrenal cortical extract were injected intravenously into twenty patients, of whom eleven exhibited elevated diastolic pressures and nine did not.

2. Of these substances only DCA acted as a pressor substance and then only in hypertensive subjects. Its pressor effect was prolonged.

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REFERENCES

1. Selye, F. L. Biochemical changes in hypertension. *Canad. M. A. J.*, 57: 325, 1947.
2. Perera, G. A. The relationship of the adrenal cortex to hypertension. *J. A. M. A.*, 129: 537, 1945.
3. Perera, G. A. and Blood, D. W. Pressor activity of desoxycorticosterone acetate in normotensive and hypertensive subjects. *Ann. Int. Med.*, 27: 401, 1947.

* Supplied by Schering Corporation.
† Supplied by Parke, Davis & Company.

4. Perera, G. A., Knowlton, A. I., Lowell, A. and Loeb, R. F. Effect of desoxycorticosterone acetate on the blood pressure of man. *J. A. M. A.*, 125: 1030, 1944.
5. Perera, G. A. and Blood, D. W. A comparison of the pressor activity of desoxycorticosterone acetate in normotensive and hypertensive subjects. *Proc. Am. Soc. Clin. Investigation*, 1947.
6. Hamilton, W. F., Brewer, G. and Brotman, I. Pressure pulse contours in the intact animal. *Am. J. Physiol.*, 107: 427, 1934.
7. McGavack, T. H. and Vogel, M. Propylene glycol as a menstruum for the administration of steroid hormones. *J. Lab. & Clin. Med.*, 29: 1256, 1944.
8. Goldman, M. L. and Schroeder, H. A. The immediate pressor effect of desoxycorticosterone acetate. *Science*, 107: 272, 1948.

Prolongation of the Coagulation of Whole Blood by Dicumarol in Man*

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USE of dicumarol for the prevention of intravascular clotting has become increasingly widespread in clinical practice.[1] While it is well established that dicumarol in adequate amounts causes prolongation of the blood prothrombin time, it has little influence on the clotting time of whole blood as carried out in glass tubes until the prothrombin clotting time has been greatly prolonged.[2] Thus it has been difficult to explain the prevention of intravascular clotting by dicumarol in amounts which fail to alter significantly the whole blood clotting time and cause only a moderate decrease in the prothrombin clotting time, particularly since Quick[3] has shown that much lower prothrombin levels are necessary to inhibit clotting *in vitro*.

However, an increasing number of reports have indicated the effectiveness of comparatively small doses of dicumarol in preventing thrombosis.[4,5] Such clinical observations raise the question of whether or not dicumarol influences the coagulation of blood in a manner which is not accurately reflected by the prothrombin clotting time or by the clotting time of whole blood in glass tubes. In the investigation herein reported this problem has been studied employing glassware coated with a silicone (drifilm)‖ following the method described by Jaques and co-workers.[6]

METHODS AND MATERIALS

Studies were carried out in a group of eleven male and female patients, of whom seven had multiple sclerosis, one had Friedreich's ataxia and three had generalized arteriosclerosis. In most cases dicumarol was given orally in dosage of 300 mg. the first day, 200 mg. the second day and thereafter usually reduced to 100 mg. a day.

Prothrombin clotting times were carefully performed using Quick's method[3] and employing 0.020 M calcium chloride solution. Rabbit brain thromboplastin was used and a dilution curve for control plasma was plotted. The prothrombin clotting time was reported in per cent of normal.

Whole blood clotting time was determined by a modification of the method of Lee and White.[7] Blood was obtained with a swift, clean venipuncture using a sharp No. 19 needle; very little tourniquet pressure was used and the patient was bled without use of a syringe. Discarding the first portion, the free-streaming blood was allowed to flow down the inside of a 100 by 16 mm. plain glass tube, avoiding bubbles and agitation. The tubes were immediately placed in the water bath at 37°C.

The clotting time in glass, as measured by an end point of definite jelling of the blood, was from five to twelve minutes in normal controls and in patients before dicumarol therapy. Occasionally, using this technic, a clotting time up to fifteen minutes was observed in healthy controls; for the purposes of this paper an arbitrary limit of clotting time of over fifteen minutes in glass at 37°C. was considered abnormal.

‖ This material was supplied by the Research Division of the General Electric Co. (General Electric Drifilm No. 9987.)

* From the Clinical Research Laboratory, Holy Ghost Hospital, Cambridge, Mass. This study was supported by a grant from the American Cancer Society and is part of an investigation on blood coagulation in malignant diseases.

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Bleeding into drifilmed tubes was carried out exactly as done for the glass tubes. The glass tubes were carefully coated with drifilm but variable results were obtained if the tubes were redrifilmed after use; in this study tubes were drifilmed and used only once. The quality of

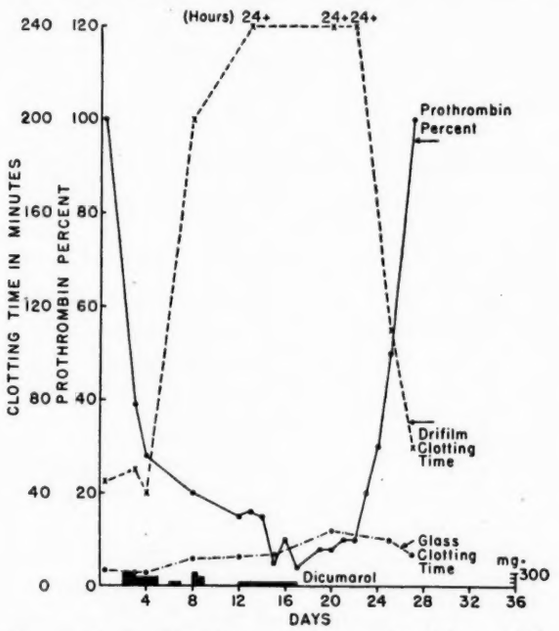

FIG. 1. F. C., fifty-three, a white male with multiple sclerosis. Graph illustrating the marked prolongation of the clotting time in drifilm tubes compared to the clotting time in glass tubes following the administration of dicumarol.

the water caused a marked difference in the drifilm surface. On one occasion when tap water instead of distilled water was used in preparation of the tubes, the procedure was completely spoiled. It was found that results were just as accurate without drifilming the needles and better tests were obtained when the use of drifilmed syringes was discontinued.

The temperature at which the drifilm clotting times were carried out greatly influenced the clotting time. Jaques and his associates[6] found that at ice box temperature blood remained unclotted for many hours in drifilm and this finding was repeatedly confirmed in our experience. At room temperature clotting times were longer but more variable than at body temperature. Hence in this work the clotting studies were carried out in a water bath at 37°C. In normal controls the clotting time of whole blood in drifilm varied from thirty to sixty minutes and a clotting time of over sixty minutes at 37°C. was considered abnormally prolonged. Since contamination with tissue juice causes remarkably decreased clotting time in drifilm and invalidates the clotting tests,[6] with a poor or difficult venipuncture the test was discarded and a fresh venipuncture was carried out.

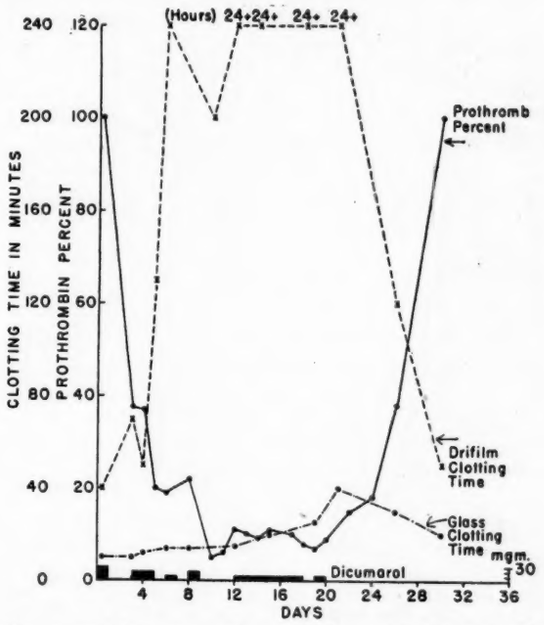

FIG. 2. C. M., seventy-five, a white male with generalized arteriosclerosis. Demonstrating the effect of dicumarol on the clotting time of whole blood in drifilm tubes as compared to glass tubes.

RESULTS

As indicated in Figures 1 to 4, following administration of dicumarol, an increase in the prothrombin clotting time usually occurred within forty-eight hours but the degree of hypoprothrombinemia varied considerably. The clotting time in drifilm became definitely prolonged after forty-eight hours and when 700 mg. to 900 mg. of dicumarol were given over a seven-day period, prolongation of the drifilm clotting time for periods of from twenty-four to seventy-two hours or longer was observed. At the same time the clotting of whole blood in glass was prolonged slightly or not at all until very marked depletion of prothrombin occurred.

COMMENTS

Clotting of blood as observed in glass represents an artificial and false reflection

of the true state of intravascular blood coagulability. In the past, paraffin, collodion and plastics such as lusteroid have been employed to simulate more closely the endothelial surface.[8,9] Davidson and MacDonald[2] observed that in patients given massive doses of dicumarol, the clotting time of whole blood in lusteroid was much more prolonged in relationship to the fall in prothrombin clotting time than was the clotting time in glass. Although there was a marked variability of the clotting time in lusteroid, these authors concluded that the coagulation time in lusteroid indicated the true coagulation defect more closely than did glass.

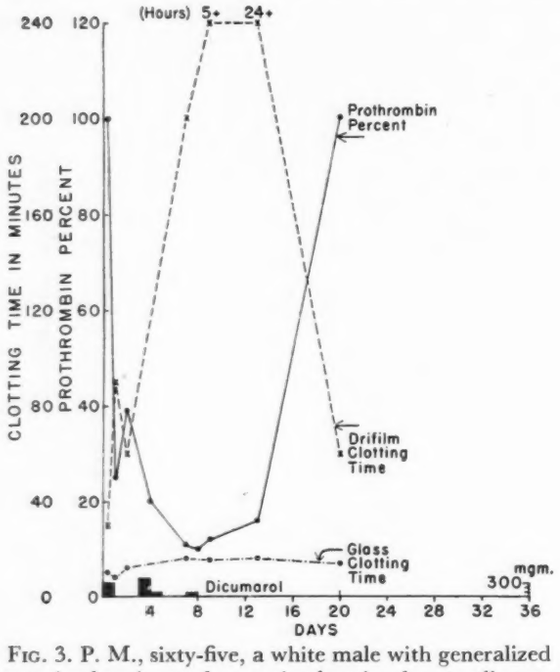

FIG. 3. P. M., sixty-five, a white male with generalized arteriosclerosis and arteriosclerotic heart disease. Graph illustrating the prolongation of clotting time in drifilm tubes compared to normal clotting time in glass tubes.

The recent work of Jaques and his coworkers[6] on the effect of a silicone in prolonging the clotting time offers a new method for the study of blood coagulation. With certain modifications, as just noted, the silicone technic was employed in this study of the effect of dicumarol on the clotting mechanism As a result it was demonstrated that at prothrombin levels which were not low enough to influence the clotting time in glass, dicumarolized blood in drifilmed tubes took twenty-four hours or longer to clot. These observations provide laboratory support, hitherto lacking, for the accumulating clinical evidence that dicumarol may be effective in prevention of intravascular clotting even in dosages which are inadequate to produce critically low prothrombin activity or prolongation of the clotting time in glass.

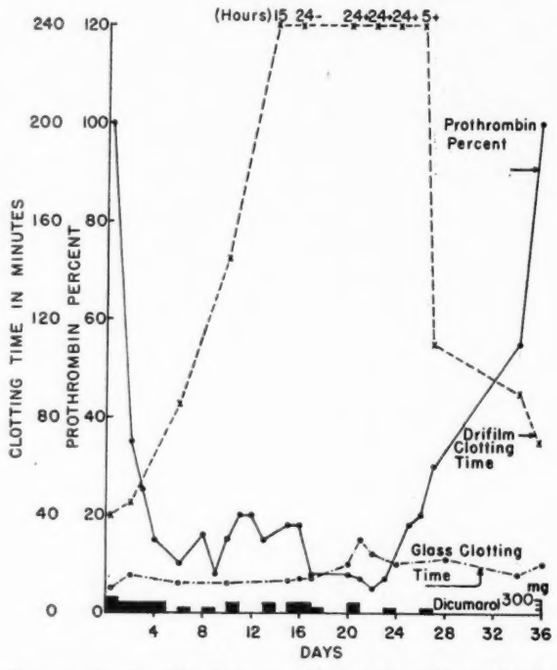

FIG. 4. R. K., fifty-five, a white male with multiple prolongation of the clotting time of whole blood in drifilm tubes and the delayed moderate elevation of the clotting time in glass tubes following the administration of relatively large amounts of dicumarol.

From the clinical standpoint the estimation of clotting time as carried out in glass tubes is of little practical value in the management of the dicumarolized patient. Clotting tests in drifilm require rather exact technic and for routine use would not be a practical method at present. However, development of a plastic necessitating less care in preparation of the tubes and providing a more permanent surface will undoubtedly extend the usefulness of this type of material in the study of blood coagulation. In our present state of knowledge the careful determination of the prothrombin

clotting time is the best laboratory method of controlling the clinical use of dicumarol.

SUMMARY

1. Dicumarol administered to a series of eleven patients caused a greatly prolonged clotting time of whole blood in drifilmed tubes. The clotting time in glass tubes did not accurately reflect this coagulation defect.

2. The data presented support the clinical impression that intravascular clotting may be prevented, at least in part, by amounts of dicumarol which fail to depress the prothrombin activity of the blood to levels hitherto considered necessary for the inhibition of clotting.

REFERENCES

1. Allen, E. V. Challenge of thrombosis and embolism of blood vessels and clinical use of anticoagulants. *Quart. Bull., Northwestern Univ. M. School*, 20: 1–7, 1946.
2. Davidson, C. S. and MacDonald, H. A critical study of the action of 3–3 methylenebis (4-hydroxycoumarin) (dicoumarin). *Am. J. M. Sc.*, 205: 24–33, 1943.
3. Quick, A. J. The Hemorrhagic Diseases and the Physiology of Hemostasis. Springfield, Ill., 1942. Charles C. Thomas, Publisher.
4. Evans, J. A. The prevention of postoperative pulmonary embolism. *New England J. Med.*, 236: 392, 1947.
5. Peters, H. R., Guyther, J. R. and Brambel, C. F. Dicumarol in acute coronary thrombosis. *J. A. M. A.*, 130: 398, 1946.
6. Jaques, L. B., Fidlar, F., Feldsted, E. T. and MacDonald, A. G. Silicones and blood coagulation. *Canad. M. A. J.*, 55: 26–31, 1946.
7. Lee, R. I. and White, P. D. A clinical study of the coagulation time of blood. *Am. J. M. Sc.*, 145: 495–503, 1913.
8. Lozner, E. L. and Taylor, F. H. L. The effect of foreign surfaces on blood coagulation. *J. Clin. Investigation*, 21: 241–245, 1942.
9. Tocantins, L. M. Influence of the contacting surface on the coagulability and anti-cephalin activity of normal and hemophiliac plasmas. *Am. J. Physiol.*, 143: 67, 1945.

Thephorin in Allergy*

A Study of 292 Cases

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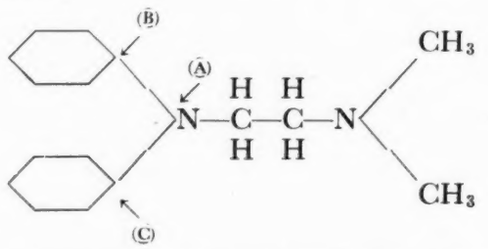
THE history of the development of antihistaminic compounds has been reviewed by Feinberg.[1] A description of anaphylaxis and of the parallelism between its symptoms and those of certain allergic states was accomplished over fifty years ago, and eventually led to the application of specific desensitization procedures in clinical allergy. Research has more recently turned to the discovery of a method which would inhibit the anaphylactic or allergic process without recourse to the use of specific antigens. In 1932 Hill and Martin[2] reported that until that date 165 substances or technics had been investigated for such non-specific inhibition. Among them were bizarre therapeutic agents, including benzene in large doses, low atmospheric pressures and extracts and cultures of Mycobacterium tuberculosis. Also tried were atropine, ether, chloral hydrate, barium and many non-specific sera and proteins. In 1944 Feinberg[3] listed many other methods; among them were the barbituric acid derivatives, salts of sodium and potassium, vitamin C, vitamin P (hesperidin) and ethylene disulfonate, all tried and found wanting.

Workers in allergy are generally agreed that chemical agents common to all anaphylactic and allergic reactions must be responsible for the clinical signs and symptoms; the picture produced falls into one of a few predictable patterns no matter which of a great variety of antigens is applied to the sensitized organism. A long series of investigations has led to the conclusion that histamine is one such chemical agent and may be, in part, responsible for the clinical manifestations observed in allergic individuals.

Direct attacks on the histamine factor in the allergic reaction have followed a logical pattern. First, desensitization by injection of small amounts of histamine itself was tried. Review of clinical and laboratory investigations into this technic suggests that its usefulness, if any, is limited.[4–7] Since injection of histamine failed to produce antihistaminic substances, it was hoped that a protein-histamine conjugate might stimulate the formation of antibodies. A variety of proteins, ranging from casein to dog serum, has been linked to histamine; however, the investigations reported to date fail to prove that the use of these conjugates materially increases immunity or histamine tolerance.[8–11] Finally, a histamine-destroying enzyme, histaminase, was tried. Feinberg[1] reviewed thirty contributions to the literature on histaminase and suggested that its efficacy *in vitro* had not been duplicated *in vivo*.

Several chemical agents which seem to compete with histamine in biochemical reactions have shown promise in the symptomatic relief of the allergies. Four of the most effective compounds, two French (antergan and neoantergan) and two American (benadryl and pyribenzamine) have the same basic structural formula:



In benadryl an ether linkage is substituted for the nitrogen atom at (A). Pyribenzamine

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has a carbon atom added at (B) and a nitrogen atom substituted for the carbon at (C). Thephorin,* the drug employed in the present investigation, is a polycyclic amine, the empiric formula of which is $C_{19}H_{19}N$. The laboratory investigations of the antihistaminic action of thephorin which have been recorded[12] and two preliminary reports of the clinical efficacy of the drug[13,14] suggest that it merits careful clinical evaluation.

Reports of clinical investigations of antihistaminic agents are difficult to evaluate and almost impossible to compare. Some workers have been content to report a percentage of patients "improved" or "unimproved" without trying to quantitate the change. Allergic manifestations are prone to cyclic changes. The phenomena under consideration lend themselves poorly to objective analysis. In November, 1946, in a report to the Council on Pharmacy and Chemistry of the American Medical Association,[1] the following criteria were suggested to test the effectiveness of a symptomatic remedy in allergic disease:

"1. Unquestioned relief of symptoms must be obtained on the administration of the drug on repeated occasions.

"2. Recurrence of symptoms should follow the discontinuance of the medicament.

"3. The relief should be obtained under conditions sufficiently controlled and under varying circumstances so that it cannot be attributed to normal fluctuations in tolerance or to external factors such as weather or pollen concentration.

"4. Wherever possible, objective changes should confirm subjective claims.

"5. Placebo medication should fail to produce relief."

The present study falls short of the mark in several of these categories.

In this investigation, 292 allergic patients were followed during the year 1947. The effect of medication was charted on weekly visits to the allergy clinic. Quantitation of subjective response was attained by training patients to think in terms of severity and frequency of attacks. If asthmatic seizures were less than one-half as severe immediately after medication was begun, 50 per cent relief was recorded; if less than one-half as frequent, 50 per cent relief was recorded; if both, 75 per cent relief was recorded. Although placebos were not used, 142 patients were treated with thephorin and other antihistamine drugs alternately and they were asked to compare results.

* Brand of Phenindamine (2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate) supplied by Hoffmann-La Roche, Inc., Nutley, N. J. Thephorin Trade Mark Reg. U.S. Patent Office.

TABLE I

SIDE REACTIONS TO THEPHORIN IN 54 OF 292 PATIENTS

Gastrointestinal	19
*Nausea and vomiting	(4 patients)
*Constipation	(3 patients)
Abdominal pain	
Thirst	
Anorexia	
Nervous	33
*Stimulation	(2 patients)
*Weakness	(2 patients)
Insomnia	
Palpitation	
Drowsiness	
Headache	
Urticaria	1
Urinary urgency and frequency	1

* These eleven patients discontinued medication for the reasons indicated by asterisk. All other reactions were readily controlled, or sufficiently mild to permit uninterrupted treatment with thephorin.

Eighty-three cases of asthma were observed; of these, fifty-eight were studied in some detail. The majority were extrinsic (forty-four), the minority intrinsic or bacterial (fourteen). Ages ranged from two to seventy-one; the weight distribution followed a normal curve. There were thirty-one males and twenty-seven females. The duration of the disease was over twelve years in 60 per cent of the cases. Thirty had previously used benadryl, eighteen with unpleasant side reactions. Twenty-four had previously used pyribenzamine, seven with unpleasant side reactions. Of the eighty-three asthmatics on thephorin, eighteen had reactions, four of these requiring discontinuance. (Table I.) Comparison of the efficacy of thephorin with that of other drugs used was most interesting. Of twenty-one asthmatic patients alternating with pyribenzamine, sixteen thought thephorin

more effective, three thought them equally effective and two preferred pyribenzamine. Of twenty-four alternating with benadryl, seventeen thought thephorin better, six reported the two drugs to be equally effective and one preferred benadryl. It must be borne in mind in making such comparisons that this series is heavily weighted in favor of thephorin, in that many patients volunteered for the experiment because they were dissatisfied with their response to one of the other antihistaminic drugs. Percentage of relief for the asthmatic patients was recorded as follows: 0 to 49 per cent relief, twenty-six; 50 to 74 per cent relief, fifteen; 75 to 100 per cent relief, forty-two patients. (Table II.) The adequate daily dose ranged from 50 to 200 mg.

One hundred sixty-one patients with allergic rhinitis were treated with thephorin. Of these, 131 were studied in some detail. Ages ranged from two to seventy. There were seventy-four males and fifty-seven females. Duration was over twelve years in 42 per cent of the cases. Sixty-two had previously used benadryl, thirty-eight with unpleasant reactions. Forty-six had previously used pyribenzamine, eleven with unpleasant reactions. Of the 131 patients with allergic rhinitis, twenty-seven complained of side effects, but only five discontinued thephorin medication. (Table I.) Again, direct comparison with other drugs was weighted heavily in favor of thephorin. Of forty-two patients alternating with pyribenzamine, twenty-eight thought thephorin more effective, five thought them equally effective and nine preferred pyribenzamine. Of fifty-three alternating with benadryl, thirty-eight thought thephorin better, eight reported the drugs to be equally effective and seven preferred benadryl. Percentage of relief for the allergic rhinitis patients was recorded as follows: 0 to 49 per cent relief, thirty-three; 50 to 74 per cent relief, twenty-three; 75 to 100 per cent relief, 105 patients. (Table II.) The adequate daily dose ranged from 25 to 200 mg.

Other allergic conditions, such as migraine, angioneurotic edema and allergic dermatitis were treated in numbers too small to be statistically significant. These thirty-eight cases are therefore summarized without comment in the accompanying table.

TABLE II
THEPHORIN IN 292 CASES OF ALLERGY

Diagnosis	Cases	Good Result (75–100% Relief)	Fair Result (50–74% Relief)	Poor Result (0–49% Relief)
Asthma	83	42	15	26
Allergic rhinitis	161	105	23	33
Angioneurotic edema	18	13	0	5
Allergic dermatitis	18	5	4	9
Migraine	12	8	0	4

SUMMARY

1. A new antihistaminic drug, chemically unrelated to others now available, was employed in the management of 292 allergic patients.

2. The symptomatic relief observed and the paucity of untoward reactions reported suggest that this drug deserves extensive clinical trial.

REFERENCES

1. FEINBERG, S. M. Histamine and antihistaminic agents; their experimental and therapeutic status. *J. A. M. A.*, 132: 702–713, 1946.
2. HILL, J. H. and MARTIN, L. A review of experimental studies of nonspecific inhibition of anaphylactic shock. *Medicine*, 11: 141, 1932.
3. FEINBERG, S. M. Non-specific inhibition of anaphylaxis. *J. Allergy*, 15: 302, 1944.
4. ERNESTENE, A. C. and BANKS, B. M. Use of histamine in the treatment of pruritus: preliminary report. *J. A. M. A.*, 100: 328, 1933.
5. HORTON, B. T., MACLEAN, A. R. and CRAIG, W. MCK. New syndrome of vascular headache: results of treatment with histamine: preliminary report. *Proc. Staff Meet., Mayo Clin.*, 14: 257, 1939.
6. WELLS, J. A., GRAY, J. S. and DRAGSTEDT, C. A. An investigation of the question of histamine tolerance. *J. Allergy*, 13: 77, 1941.
7. BUTLER, S. and THOMAS, W. A. Intravenous histamine in the treatment of migraine; preliminary observations. *J. A. M. A.*, 128: 173, 1945.
8. SHELDON, J. M., FELL, N., JOHNSTON, J. H. and HOWES, H. A. A clinical study of histamine azoprotein in allergic disease (preliminary report). *J. Allergy*, 13: 18, 1941.

9. Cohen, M. B. and Friedman, H. J. Antibodies to histamine induced in human beings by histamine conjugates. *J. Allergy*, 14: 195, 1943.
10. Fell, N., Rodney, G. and Marshall, D. E. Histamine-protein complexes: synthesis and immunologic investigation. I. Histamine azoprotein. *J. Immunol.*, 47: 237, 1943.
11. Coffin, G. S. and Kabat, E. A. The effects of immunization with histamine azoprotein on histamine-intoxication and passive anaphylaxis in the guinea pig. *J. Immunol.*, 52: 201, 1946.
12. Lehmann, G., Hagan, E., Barbarow, G. and Roe, M. The antihistamine action of pyridindene derivatives. *Federation Proc.*, 6: 350, 1947.
13. Davis, H. P. and Mowry, W. A. A preliminary report on the use of nu-1504. Read before the Chicago Society of Allergy, May 19, 1947.
14. Reynolds, J. L. and Horton, B. T. Clinical observations on the use of thephorin (nu-1504): a new antihistaminic agent. *Proc. Soc. Clin. Research*, 20: 83, 1947.

Agranulocytosis during Propylthiouracil Therapy*

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BEFORE a conclusion is justified as to the incidence of reactions of any new drug treatment of many patients is necessary. In our use of thiouracil it was determined after treating 400 patients that reactions occurred in 9 per cent of the subjects. Since no difficulty was encountered during treatment of the first forty-five patients, the conclusion could have been reached that thiouracil could be administered without danger. Among the next ten patients treated, agranulocytosis occurred in three cases which forcibly indicated that there was real danger in administering thiouracil.

The initial report on the use of propylthiouracil in hyperthyroidism by Astwood and Vander Laan dealt with the treatment of one hundred patients. As they observed no significant side effects they gained the impression that propylthiouracil was a completely safe drug. Baird, in a critique on thyroidectomy in hyperthyroidism, used the absence of reactions to propylthiouracil as strong evidence in favor of drug therapy. He reported that in several thousand patients treated with propylthiouracil only a few minor reactions occurred and in no patient was it necessary to discontinue the drug. Reveno observed fifty-four hyperthyroid patients treated with propylthiouracil. In no instance was there an alteration in the leukocytes. Fever developed in one patient after forty-one days of therapy; a test dose one week after withdrawal of propylthiouracil caused recurrence of fever in four hours, showing definite sensitivity.

A serious reaction following propylthiouracil therapy was reported by Livingston and Livingston. Agranulocytosis and hepatocellular jaundice developed in this patient after six weeks of treatment with propylthiouracil in a daily dosage of 150 to 200 mg. The peripheral blood and bone marrow revealed an absence of granulocytes; the leukocyte count was 1,050. Recovery followed intensive therapy with penicillin and streptomycin. A case in which moderate leukopenia (2,100 cells) and granulocytopenia (22 per cent) developed was reported by Eisenmenger and Steele. Changes in the blood took place after four months of propylthiouracil in a daily dose of 150 to 200 mg. Previously moderate leukopenia (3,400 cells) and granulocytopenia (40 per cent) had developed in this patient after six months of therapy with thiouracil.

There were seven toxic reactions among 218 hyperthyroid patients treated by McCullagh and his associates. These reactions consisted of nausea, arthralgia and numbness of the extremities which were not severe enough to require stoppage of therapy. In four patients, treatment was discontinued because of the development in each case of either severe exfoliative dermatitis, numbness of the extremities, granulocytopenia of 25 per cent or urticaria. Since they had not observed agranulocytosis, they discontinued weekly blood counts and advised blood studies only in the event of sore throat. McGavack encountered but one reaction to propylthiouracil in seventy-five patients. This consisted of fever and generalized rash after nine days on a dose of 50 mg. of propylthiouracil daily. A similar reaction occurred after five days of treatment with thiouracil. Williams treated thirty-nine thy-

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rotoxic patients with propylthiouracil and in no patient did a reaction develop. Two of the patients treated had previously shown a reaction to thiouracil (a rash in one case and leukopenia and rash in the other).

TABLE I
REVIEW OF REPORTS FROM THE LITERATURE

Authors	No. Patients Treated	Reactions		
		Type	No.	Per Cent
Astwood-Vander Laan	100	Urticaria	2	2.0
Reveno	54	Fever	1	1.8
McCullagh-Hibbs-Schneider	218	Nausea	1	
		Arthralgia	1	
		Numbness of extremities	2	
		Severe dermatitis	1	
		Granulocytopenia	1	
		Urticaria	1	
			7	3.2
McGavack et al	75	*Generalized rash with fever	1	1.3
Williams	39	0		
Total	486		11	2.0
Livingston and Livingston	?	Agranulocytosis and hepatitis	1	
Eisenmenger-Steele	?	*Leukopenia with granulocytopenia	1	
Shibley	?	Agranulocytosis	1	

* Similar reaction to thiouracil.

A review of eight reports (Table I) dealing with the use of propylthiouracil reveals agranulocytosis to have occurred twice. Granulocytopenia sufficient to warrant withdrawal of treatment occurred in two patients, generalized rash in two patients, urticaria in three and fever in one. Numbness of the extremities, nausea or arthralgia were also noted. Among 486 patients treated with propylthiouracil there were eleven reactions, an incidence of 2 per cent.

In the last four and one-half years we have used antithyroid drugs in preoperative preparation for thyroidectomy of 1,100 patients with hyperthyroidism. Four hundred of these patients received thiouracil, with a reaction incidence of 9 per cent (fever, skin eruption, depression of leukocytes, swollen salivary glands and edema of the skin). Twenty-eight patients were given thiobarbital, a very potent antithyroid agent, with a high reaction incidence of 28 per cent (depression of leukocytes and fever). The remaining 672 patients received propylthiouracil (probacil).* In this latter group there were thirteen definite reactions (Table II), an incidence of 1.9 per cent. Most of the reactions involved the blood,

TABLE II
REACTIONS TO PROPYLTHIOURACIL

A. White blood cell depression	
1. Agranulocytosis	3
2. Leukopenia, granulocytopenia or both	7
B. Fever	1
C. Skin irritation	1
D. Scleredema	1
Total reactions	13
Percentage	1.6

three patients developed agranulocytosis and seven patients either significant leukopenia, granulocytopenia, or both. Single cases of fever, skin irritations and scleredema were also observed.

The purpose of this paper is to report the observation that changes in the leukocytes occurred in 10 of 672 patients during therapy with propylthiouracil and that agranulocytosis, a serious clinical condition, occurred in three of these. The case reports of the three patients developing agranulocytosis are of chief interest, especially two of which revealed similar blood changes on shifting to thiouracil.

CASE REPORTS

CASE 1. A woman, fifty years of age, was initially seen in April, 1946, with signs and symptoms of recurrent hyperthyroidism. She had a thyroidectomy in 1929. She had lost 20 pounds in the previous year and had become extremely nervous. The thyroid remnants were moderate in size, the basal metabolic rate was +24 and the pulse rate 108.

Treatment with propylthiouracil was begun in a daily dose of 75 mg. After thirty days the dose was increased to 150 mg. daily. Blood counts were taken periodically (Fig. 1); the percentage of polymorphonuclear cells remained satisfactory but the total white counts during the fifth and sixth week were around 4,000 cells. Treatment was continued and on the sixtieth day sore throat and fever developed. Total leukocyte count at this time was 1,950, with

* Supplied by Dr. Stanton Hardy of Lederle Laboratories, Pearl River, N. Y.

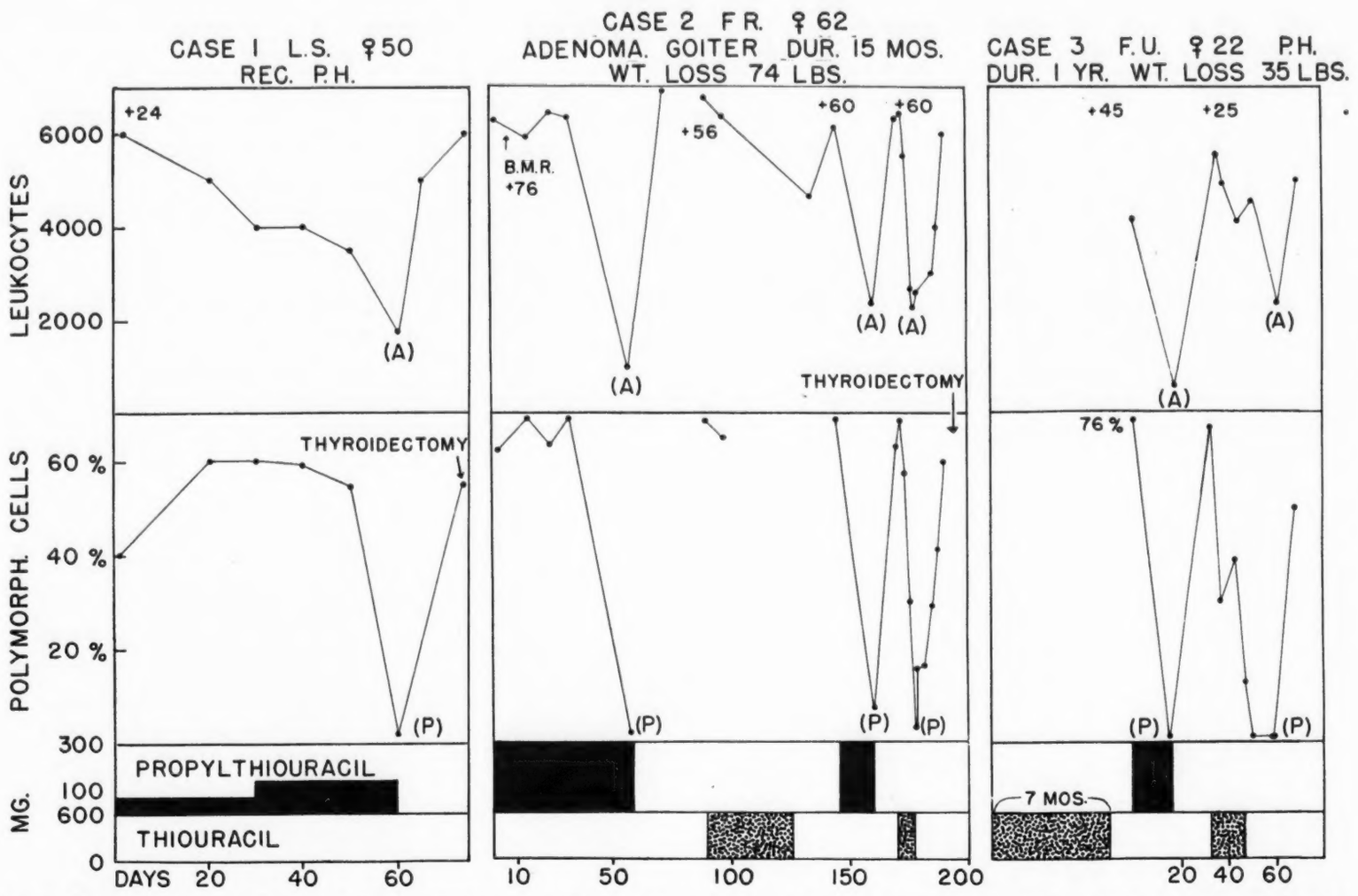

FIG. 1. Three cases of agranulocytosis following administration of propylthiouracil. Case II developed agranulocytosis three times, twice following propylthiouracil and once following thiouracil. In Case III agranulocytosis followed administration of propylthiouracil and again after thiouracil which had previously been taken for seven months.

1 per cent polymorphonuclear cells. The patient was hospitalized and given penicillin. In eight days the white blood cells returned to normal and a week later the thyroid remnants were surgically removed. The postoperative course was satisfactory.

CASE II. (Fig. 1) A woman, sixty-two years of age, was first seen in May, 1947. She had noted a lump in her neck for seven years. For fifteen months she had symptoms characteristic of hyperthyroidism and had lost 79 pounds in weight. The basal metabolic rate was +76 and the pulse rate 116 beats per minute. In addition to hyperthyroidism she had long-standing hypertension, enlargement of the heart by roentgenologic examination and the electrocardiogram showed left axis deviation.

Treatment was begun with a daily dose of 300 mg. of propylthiouracil. Progress was satisfactory, with normal periodic blood counts until the fifty-fourth day of treatment when a severe sore throat developed. Blood studies showed a leukocyte count of 1,000 with a total absence of polymorphonuclear cells. She was critically ill but recovered following penicillin therapy. In two weeks the white blood cells were normal. Three weeks later, since the patient was still markedly hyperthyroid (basal metabolic rate +56), treatment was begun with thiouracil, 600 mg. daily. She took this for thirty-six days. Treatment then was discontinued for two weeks; blood tests at this time were normal. Thiouracil was again prescribed but through a druggist's error propylthiouracil was given. Sixteen days later she was readmitted to the hospital with agranulocytosis, the white count being 2,000 cells with an absence of polymorphonuclear cells. Penicillin was administered and in fifteen days the white blood cells had returned to normal. Since the patient was still hyperthyroid, basal metabolic rate +60, it was decided to continue antithyroid treatment with thiouracil to which she had not shown any intolerance. After the administration of thiouracil, 600 mg. daily for seven days, the blood was again depressed, the white count being 2,400 and polymorphonuclear cells 4 per cent. Treatment was again instituted with penicillin and in two weeks the blood had returned to normal.

As the patient had twice shown intolerance to propylthiouracil and once to thiouracil it was thought unwise to attempt further antithyroid treatment with other available antithyroid drugs, such as methylthiouracil or thiobarbital, for fear that agranulocytosis might recur and that the bone marrow might fail to restore itself; thyroidectomy was therefore undertaken on November 28, 1947. The postoperative course was satisfactory but not as smooth as observed in patients under antithyroid control. She was discharged from the hospital on the eighth postoperative day.

CASE III. A woman, twenty-two years of age, was seen on September 22, 1947, with symptoms and signs of severe primary hyperthyroidism. (Fig. 1.) Her symptoms were of eighteen months' duration during which time she had lost 35 pounds. Diagnosis of hyperthyroidism had been made nine months before and she had taken thiouracil irregularly for seven months without control of the disease; no treatment had been taken for two months. She was poorly nourished and extremely weak. There was moderate tremor and exophthalmos. The thyroid gland (hyperplastic) was moderate in size and the basal metabolic rate was +45.

Antithyroid treatment in preparation for thyroidectomy was begun with propylthiouracil in a daily dose of 300 mg. A high caloric diet and supplemental vitamins were also prescribed. On the sixteenth day of treatment fever of 106°F. and severe sore throat developed. The leukocyte count was 600, with an absence of polymorphonuclear cells. Penicillin was promptly administered, with recovery of the patient. Leukocytes were normal in two weeks.

Since the patient was still a serious risk for thyroidectomy, weight 68 pounds and basal metabolic rate +25, it was decided to give further antithyroid treatment and as she had tolerated thiouracil for seven months this was chosen as the antithyroid drug. On the thirteenth day treatment was discontinued because of fever and sore throat and a polymorphonuclear percentage of 3. Penicillin was again administered and, because of fear of the presence of penicillin insensitive organisms, streptomycin was also given. The patient recovered with the white blood cells returning to normal in eight days.

This patient is now taking Lugol's solution and soon a final decision will be made as to whether or not additional measures are necessary to prepare her for safe thyroidectomy.*

* Since submitting this manuscript, this patient has had a two-stage thyroidectomy and has completely recovered.

SUMMARY

Reactions to propylthiouracil occurred in 13 of 672 patients (1.9 per cent), with ten of these reactions involving the blood, three leading to agranulocytosis. This experience indicates that propylthiouracil must be administered under careful supervision since serious reactions may occur following its use which need immediate treatment if complications are to be avoided.

REFERENCES

1. Astwood, E. B. and Vander Laan, W. P. Treatment of hyperthyroidism with prophylthiouracil. *Ann. Int. Med.*, 25: 813–821, 1946.
2. Baird, R. W. Treatment of hyperthyroidism. *New England J. Med.*, 236: 551–552, 1947.
3. Eisenmenger, W. J. and Steele, J. M. Leukopenia following the use of propylthiouracil. *J. A. M. A.*, 135: 510–511, 1947.
4. Livingston, H. J. and Livingston, S. F. Agranulocytosis and hepatocellular jaundice. *J. A. M. A.*, 135: 422–425, 1947.
5. McCullagh, E. P., Hibbs, R. E. and Schneider, R. W. Propylthiouracil in treatment of hyperthyroidism. *Am. J. M. Sc.*, 214: 545–552, 1947.
6. McGavack, T. H., Gerl, A. J., Vogel, M. and Schutzer, S. Clinical comparison of effectiveness of 6-n-propylthiouracil and 2-thiouracil as antithyrotoxic agents. *Am. J. Med.*, 2: 144–149, 1947.
7. Reveno, W. S. Propylthiouracil in thyrotoxicosis; observations on 54 patients. *J. A. M. A.*, 133: 1190–1192, 1947.
8. Shibley, G. S. Quoted by A. Barfred. Methylthiouracil in the treatment of thyrotoxicosis. *Am. J. M. Sc.*, 214: 349–362, 1947.
9. Williams, R. H. Antithyroid drugs; comparison of results of newer forms of treatment of thyrotoxicosis. *Arch. Int. Med.*, 80: 11–36, 1947.

Acute Porphyria*

Two Cases with Autopsy Reports

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THE name porphyria has a Greek derivation, porphros, meaning a crimson or purple color. In medical literature today it designates an obscure clinical entity involving "an inborn error of metabolism," as originally stated by Garrod. With a better understanding of the chemistry of the porphyrins, the classification of these abnormal conditions, in which various types of porphyrins are excreted, assumes a more rational form. The term hematoporphyria, as first used by Gunther,[8] is no longer accepted clinically in the strict sense, as it refers to a compound hematoporphyrin which does not occur in nature.[10,14] The term porphyria is now accepted to designate the congenital type and the intermittent acute type of disturbed metabolism, characterized by the excretion of uroporphyrins in the urine. In congenital cases Type I isomer is found and the chromogen, porphobilinogen, is absent. Regarding acute porphyria, recent work by Watson and associates[17] raises a question concerning the isolation of Waldenstroem's uroporphyrin III in pure form. They suggest that this may be a mixture of uroporphyrin I methyl ester and a heptamethyl ester, m.p. 208°. The term porphyrinuria includes those cases in which coproporphyrin Type I or Type III isomers are excreted in excess, secondary to certain other diseases or metabolic disturbances.[15,18]

Congenital porphyria, as the name implies, is often manifested early in life and occurs in males about four times as commonly as in females. The typical bullous eruption of the skin, referred to as Hydroa aestivale or vacciniforme sue aestivale, appears upon exposure to sunlight and may progress to scleroderma-like peripheral lesions. The dark colored urine and abnormal pigmentation of teeth and bones are also characteristic.[9]

In contrast to congenital porphyria, the acute type usually occurs between the second and fifth decades of life and is more common in women.[15] The excretion of urine darkened by the presence of uroporphyrins and "porphobilin" (derived from the chromogen porphobilinogen) may occur intermittently, and is often associated with the clinical exacerbations. These episodes are typified by abdominal pain with nausea and vomiting, refractory constipation, neurological and psychotic manifestations and severe muscular pain. The abdominal symptoms may so closely simulate acute appendicitis or bowel obstruction that a laparotomy has been performed, and in many cases the vomiting may be so persistent that parenteral fluids are mandatory. The neurological symptoms, so aptly described by Waldenstroem,[13] may assume such a variety of forms that he has applied to acute porphyria the epithet "la petite simulatrice." From his study of 143 cases, sixty of which had neurological symptoms, he stresses the frequency with which the mistaken diagnosis of hysteria is made. The

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variety of manifestations may range all the way from convulsions, quadriplegia, or delirium to subjective complaining and transitory paresis suggestive of psychoneurosis. A Landry's type of ascending paralysis is relatively common and may result in death from bulbar involvement. Hypertension frequently accompanies the acute episodes of porphyria.[2,3,5,6,7,10,15]

Many cases have come to autopsy but there is considerable variance in reports of the pathology found, particularly regarding changes in the nervous system. Thus, in contrast to Berg's report[3] of a normal brain and spinal cord in his case of a girl, aged twenty, Golden[7] recorded leptomeningeal thickening, glial scarring, and "a patchy loss of ganglion cells in the cortex" of a forty-seven year old male. He characterized these changes as being indicative of a parenchymatous toxi-degenerative process. Mason[9] demonstrated granular changes in the cortical nerve cells, degenerative alterations of the ganglion cells of the vagal and hypoglossal nuclei, and varying degrees of chromatolysis among the ganglion cells of the cord, particularly of the anterior horn in the lumbar area. The degeneration of the axis cylinders and myelin sheaths, with round cell infiltration, was most marked in the peripheral nerves of the lower extremities. He called attention to the lipoidal pigmentation, chromatolysis and vacuolization of the ganglion cells of the autonomic system, postulating a possible correlation with the gastrointestinal symptoms. These observations are in accord with those of Baker and Watson[2] who likewise describe moderate changes in the cerebral white matter and some degree of perinuclear and diffuse chromatolysis of the dorsal nucleus of the vagus and to a lesser extent of the facial and hypoglossal nuclei. They also noted that some of the muscle fibers had lost their striations and normal staining properties.

To date there is still no adequate explanation of the origin or point of action of the toxic substance which brings about the syndrome of intermittent acute porphyria. The chromogen porphobilinogen is apparently non-toxic, as large quantities have been isolated in a case during a remission.[2] However, the possibility that one of its derivatives, which include uroporphyrin and porphobilin, may play a rôle, must be kept in mind. Waldenstroem,[13] on the other hand, observed a case in which during an acute attack, no porphyrins could be found in the urine.

Although liver damage has been demonstrable in several cases of porphyria,[3,11] Mason and his group[9] are led to believe that this organ plays no rôle in the etiology of the offending toxin. They assume that the production of uroporphyrin and excessive coproporphyrin may be the result of faulty hemoglobin metabolism in the bone marrow. In some there is a history of indulgence in a barbiturate such as sulphonal, trional or veronal, but in many instances such an exposure, with sensitivity, cannot be demonstrated, and one must fall back on a theory of endogenous intoxication or constitutional discrepancy. From clinical data and autopsy material available at the present time, it would seem that the nervous system is most vulnerable to this toxic agent, whatever its nature.

Hematoporphyrin has been injected experimentally into animals as reported by Rask and Howell.[12] Following dosages of 58 mg. per Kg. intravenously in dogs, a very striking sequence of events was produced, provided the animals were exposed to sunlight. Manifestations of cutaneous erythema and irritation, followed by motor excitation, hyperpnea and rapid pulse, led to a terminal stupor and death in circulatory collapse. From additional perfusion experiments on terrapin hearts they con-

clude that the central nervous system effects are reflex rather than the direct result of a toxic agent produced in the skin.

In very small doses for its stimulative effect, hematoporphyrin in the form of "Photodyn" has been used as a therapeutic agent in the treatment of depressive psychoses.[1]

The two cases described below portray the typical clinical pattern ascribed to acute porphyria and the tendency to undergo remissions in spite of a poor ultimate prognosis.

CASE REPORTS

CASE 1. P. M. M., a twenty-seven year old girl, was first admitted to the Robert W. Long Hospital on March 5, 1945, because of extreme generalized weakness, difficulty in swallowing and occasional bowel incontinence. The initial symptoms of her illness, which began in October, 1944, had been psychic in nature, marked by a vague restlessness and emotional instability. Within a short time she became acutely ill with nausea, vomiting, abdominal pain and loss of weight. She was placed in an army hospital for two to three weeks, during which time there was noted a rapid loss of strength and impaired bowel function. She was transferred to Passavant Memorial Hospital in Chicago where, during a protracted stay of fourteen weeks, there had been an initial progression to complete quadriplegia with accompanying weakness of the right side of the face and difficulty in swallowing and talking. It had also been observed that the urine became a dark reddish color on standing and on demonstration of porphobilinogen, a diagnosis of porphyria was made. A gradual improvement in her condition then ensued, prior to her discharge early in March, 1945.

Physical examination at the time of her transfer to our hospital, revealed an individual in a poor state of nutrition with considerable muscular atrophy, weakness and pain in both upper and lower extremities. The temperature was 99.2°F., pulse 116, and blood pressure 120 mm. Hg systolic and 80 mm. diastolic. The reflexia of her upper extremities were present and equal, but knee and ankle jerks could not be elicited. Aside from a diminution of sensation below the elbows, the remainder of her examination was essentially normal.

Laboratory findings, during her stay in the hospital from March 5th through June 27th, showed a hemoglobin range from 10.5 to 12 Gm. The white blood cells varied between 5,000 and 8,000 with essentially normal differential counts. The serologic reaction (Mazzini) was negative and repeated sedimentation rates (Wintrobe) were 26, 37 and 24 mm. in one hour. Direct van den Bergh gave a delayed positive and the indirect showed 2.7 mg. of bilirubin. Urinalyses, aside from the dark color, were negative except for an occasional faint trace of albumin. The spinal fluid showed a white cell count of one, no red cells, negative globulin, sugar 80 mg. per cent, total protein 51 mg. per cent, and a gold curve of 10 zeros.

During hospitalization the patient was treated with hot fomentations to promote relaxation, accompanied later by tendon stimulation and muscle reeducation. She had recovered from the incontinence and regained her strength so that she could walk with support and could use her hands to write and to feed herself when she was discharged the latter part of June, 1945. This improvement had continued when she was seen in our out-patient department in August, 1945, and again in January, 1946. Two weeks after her last visit she became actuely ill with nausea and vomiting, fever, low abdominal pain and obstipation for five days. A laparotomy, performed at her local hospital, revealed a ruptured appendix with peritonitis. Her postoperative course was stormy and during her convalescence there was a recurrence of generalized weakness and pain in her extremities, accompanied finally by persistent vomiting. She was readmitted to our hospital on May 28, 1946, because of her alarming nutritional state. Upon examination one was impressed by the extreme degree of cachexia and debilitation. She could not speak above a low whisper but her faculties were unimpaired. At this time her temperature was 100.3°F., pulse 120, and blood pressure 138 mm. Hg systolic and 110 mm. Hg diastolic. There was almost complete flaccid paraplegia with pronounced muscle atrophy and a large decubitus ulcer was present over the sacrum. The abdomen was slightly distended

and tender to palpation but auscultation revealed scattered bowel sounds. The white blood count was 15,300 with 17 band cells, 65 neutrophiles, 17 lymphocytes and 1 monocyte. Blood non-protein nitrogen was 21 mg. per cent. The urine was consistently dark colored, often with a reddish tinge, and was strongly positive for porphobilinogen by the test of Watson and Schwartz.[16] She was given parenteral fluids, supportive treatment with vitamins, and penicillin, with no response. She suffered from persistent nausea and vomiting and almost constant muscular pain. Her pulse remained elevated between 115 and 140 and her temperature reached 100 or 101°F. almost daily. Her downhill course was terminated by death in respiratory failure on June 12, 1946.

An autopsy was performed and gross examination revealed the presence of consolidation and edema in both lungs and a generalized acute peritonitis. Upon histological examination the following pertinent abnormalities were noted: The acini of the thyroid were compressed by a connective tissue stroma into which had infiltrated many lymphoid cells. In some areas all traces of colloid were obliterated, warranting a microscopical diagnosis of stroma lymphomatosa. Neurotrophic degeneration of skeletal muscle was manifested by variation in size of individual fibers and loss of cross striations. The cortical white brain substance revealed a moderate deposit of yellow pigment in the perivascular structures, particularly in the frontal lobes. In the spinal cord the neurone bodies of the anterior horn cells showed some tendency toward shrinkage and pyknosis. Sections of the peripheral nerves manifested the most constant and severe alterations; nerve bundles were irregular in outline and shrunken, and there was marked demyelinization.

It is of interest to note that the younger sister of this patient is afflicted with acute porphyria, though of a milder degree without neurological manifestations. At the age of twenty-four, in 1944, she had an episode of protracted nausea and vomiting which was relieved following the administration of parenteral fluids. A second attack, similar to the first, occurred in March, 1946, at which time she was told porphyrins were found in the urine. She made a good recovery without symptoms of paralysis. A specimen of urine checked in our laboratory revealed the presence, in abundance, of porphobilinogen, thus substantiating the diagnosis.

Case II. E. L., a twenty-six year old housewife, was admitted to the Robert W. Long Hospital on February 2, 1942, complaining of a burning sensation in the suprapubic region of one week's duration, urinary frequency, nausea and vomiting. In April of 1940, because of low abdominal pain, an appendectomy had been performed. During her postoperative course, which was complicated by cystitis, it had been noted that her urine became a deep brown color on standing. In the past two years she had felt well and there had been no recurrence of abdominal distress, although the color change in the urine had persisted. Renal function tests in March, 1941, were within normal limits.

Physical examination revealed a relatively slender individual, suffering from considerable discomfort, but not acutely ill. The temperature was 99.3°F., pulse 90, and blood pressure 110 mm. Hg systolic and 90 mm. Hg diastolic. The only pertinent findings included tenderness to pressure over the bladder area and both costovertebral angles. The heart was of normal size, there were no murmurs present and the rhythm was regular. The lungs showed no demonstrable abnormality. Reflexia were present and physiological.

Laboratory findings showed that repeated urinalyses frequently contained red blood cells, many pus cells and a trace of albumin. Urea clearance, checked in March, was 34 per cent of normal. Blood studies, during her hospital stay: hemoglobin ranging from 11 to 14 Gm; white blood cells as low as 3,000, but usually between 6,000 and 7,000, with normal differential counts; sedimentation rate (Wintrobe) 21 mm.; and serology (Klein and Mazzini) normal. Spinal fluid showed a normal pressure, no cells, sugar 74 mg. per cent, total protien 22 mg. per cent, and a gold curve of 10 zeros.

Estimation of liver function by galactose tolerance test gave an excretion of 3 Gm. of galactose in five hours. Following intravenous administration of bromsulphthalein, 85 per cent of the dye was retained outside the blood after sixty minutes. The icteric index was 6, and both direct and indirect van den Bergh were negative. Special examination of the urine revealed the presence of uroporphyrin Type III as determined on a basis of its solubility and fluorescent properties by methods referred to by Dobriner and Rhoads.[4]

Because of the severe degree of cystitis present, a catheter was anchored for frequent lavage and she was given sulfathiazole by mouth. She first complained of muscular weakness and an aching sensation in her arms and thighs on March 7th. This became progressively worse so that within a week she was unable to hold a glass of water or feed herself. Concomitantly she developed a marked degree of despondency and discouragement. On March 19th, neurological examination revealed absent biceps, triceps, pronator, and supinator reflexes bilaterally, hypoactive knee jerks and normal ankle jerks. She was allowed to go home for a furlough but returned within ten days because of increasing muscular weakness and pain, difficulty in swallowing and abdominal discomfort. Following readmission her course was progressively downhill. Her blood pressure varied between 105/75 and 120/100. Difficulty in phonation and swallowing became more marked prior to her death on June 7, 1942.

The autopsy report showed that the only gross pathological condition was bilateral pulmonary congestion. Microscopically, the following pertinent pathological changes were noted: The liver showed severe albuminous degeneration and passive congestion. Sections of the spleen revealed an early amyloidosis. No significant changes were observed in the spinal cord, but degeneration of the myelin sheaths in the right sciatic nerve could be demonstrated. Permission for examination of the brain was not obtained.

SUMMARY

Two cases of acute porphyria are described with particular reference to the general course of the disease and to the findings demonstrable at autopsy. Both cases were characterized by rather typical exacerbations and remissions of symptoms referable primarily to the nervous system and to the gastrointestinal tract. The familial tendency was demonstrated in the first case. Histological study of tissues revealed the most significant changes in the peripheral nerves in which demyelinization was the outstanding feature. Loss of striations in skeletal muscle accompanied the neurological abnormalities. The identity and source of this toxic agent, as well as an interpretation of the pathogenesis of this type of disturbed metabolism, is still being sought.

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REFERENCES

1. Angus, L. R. The hematoporphyrin treatment of depressive psychoses. *Am. J. Psychiat.*, 92: 877, 1936.
2. Baker, A. B. and Watson, C. J. The central nervous system in porphyria. *J. Neuropath. & Exper. Neurol.*, 4: 68, 1945.
3. Berg, M. Acute porphyria: clinical and pathologic observations. *Arch. Int. Med.*, 76: 335, 1945.
4. Dobriner, K. and Rhoads, C. P. The porphyrins in health and disease. *Physiol. Rev.*, 20: 416, 1940.
5. Eliaser, M., Jr. and Kondo, B. O. Electrocardiographic changes associated with acute porphyria. *Am. Heart J.*, 24: 696, 1942.
6. Fetter, F., Humphrey, A. A. and Longenecker, C. R. Acute idiopathic porphyria. Report of a case. *U. S. Nav. M. Bull.*, 43: 349, 1944.
7. Golden, L. A. Hematoporphyrinuric neuritis. *Am. J. M. Sc.*, 206: 474, 1943.
8. Gunther, H. Die Hämatoporphyrie. *Deutsches. Arch. f. klin. Med.*, 105: 89, 1912.
9. Mason, V. R., Courville, C. and Ziskind, S. The porphyrins in human disease. *Medicine*, 12: 355, 1933.
10. Nesbitt, S. Acute porphyria. *J. A. M. A.*, 124: 286, 1944.
11. Nesbitt, S. and Watkins, C. H. Acute porphyria. *Am. J. M. Sc.*, 203: 74, 1942.
12. Rask, E. N. and Howell, W. H. The photodynamic action of hematoporphyrin. *Am. J. Physiol.*, 84: 363, 1928.

13. WALDENSTROEM, J. Neurological symptoms caused by socalled acute porphyria. *Acta psychiat. et neurol.*, 14: 375, 1939.
14. WATSON, C. J. The Porphyrins and Their Relation to Disease: Porphyria. 4 (Part 2), 228 (1–34), New York, 1940. Oxford Med.
15. WATSON, C. J. Porphyria. *South. M. J.*, 36: 359, 1943.
16. WATSON, C. J. and SCHWARTZ, S. A simple test for urinary porphobilinogen. *Proc. Soc. Exper. Biol. & Med.*, 47: 393, 1941.
17. WATSON, C. J., SCHWARTZ, S. and HAWKINSON, V. Studies of the uroporphyrins. *J. Biol. Chem.*, 157: 345, 1945.
18. WELCKER, M. L. The porphyrins. *New England J. Med.*, 232: 11, 1945.

Spontaneous Mediastinal Emphysema and Pneumothorax

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DRAMATIC in onset, alarming in subsequent manifestations yet in the great majority of instances carrying an excellent prognosis, spontaneous mediastinal emphysema and spontaneous pneumothorax, whether occurring independently or in association, offer an arresting problem to the diagnostician. The two disorders may be considered together so alike are they in their presumptive etiology, symptomatology and clinical course. Indeed, the case to be presented is but one of many in the literature in which the two disorders have occurred together.[1–15] The subject is important for several reasons: The conditions are more common than hitherto suspected and lend themselves to confusion with far more serious afflictions. Last, they of themselves are relatively harmless, a fact which if generally appreciated would save many man hours of work and many anxious reflections.

CASE REPORT

On August 3, 1946, Dr. J. G., a twenty-three year-old dentist, was seized with a severe stabbing pain in the lower left chest near the sternum which awoke him from a sound sleep. Except for working rather late at his office he had undertaken no unusual exertion during the preceding day nor did he recall any respiratory infection. The pain increased in intensity during the next twelve minutes, radiating through to his back, beneath the left shoulder blade and thence up to the suprascapular region. Deep breathing or coughing greatly accentuated the pain, and the patient found it necessary to sit in a semi-upright position in order to get his breath. He was seen almost immediately by his family physician who was unable to detect any changes in heart or breath sounds. One-half gr. of morphine during the next eight hours was almost entirely ineffective in controlling the pain. After the physician left the patient was startled to hear a loud clicking sound emanating from his left chest. Lasting for nearly two hours, the clicking was said to be audible halfway across the room. Next morning, some eight hours after onset of the illness, the patient was hospitalized for study.

Following an unusually heavy day's work a year and a half ago, the patient suffered a sudden attack of severe pain in the left chest radiating through to his back in the manner of the present attack. Several hours after onset of the pain he heard a loud clicking noise, apparently originating in his left chest. For twenty-four or thirty-six hours after beginning the pain continued to be severe and was made worse by abrupt changes in body position. Nevertheless the patient continued work and it was not until two weeks had gone by that he consulted his doctor. Once home he was hospitalized and given a two weeks' course of penicillin for pericarditis. At that time a rough to-and-fro murmur was audible over the apex of the heart; the murmur was doubtless considered a pleuropericardial friction rub. Chest x-ray showed only a small calcified Ghon lesion near the hilum of the left lung. There was no evidence of constitutional disturbance, such as fever, tachycardia or leukocytosis, throughout the hospital stay. Following his discharge, the patient remained asymptomatic, partaking of vigorous sports such as hunting, fishing, running and cycling, all without noticeable handicap.

In 1943 the patient had severe pain in the left chest for about twelve hours. He remained in bed a day or two but continued his duties thereafter. There was no past history of rheumatic fever or scarlet fever. The patient recalls no trauma to the chest. Frequent x-rays of the chest over the past few years disclosed no evi-

dence of tuberculosis. Yearly tuberculin tests had been weakly positive.

Physical examination showed a well developed, well nourished, somewhat slender, young, white man in no distress as long as he remained propped in a semi-upright position. Changes of position, however, caused him to grimace with pain. The temperature was 98°F., pulse, 80, respirations, 24 and blood pressure, 106/70. Findings of interest were confined to the chest. Breathing was shallow and respiratory excursions were generally limited but no asymmetry was detected. Upon percussion there was hyper-resonance over the sternum and adjacent precordial region. The heart borders could not be accurately mapped out. Auscultation of the chest revealed diminished breath sounds and vocal fremitus over the left chest posteriorly down to about the sixth rib. Over the precordium extending from a point just to the right of the sternum around to the posterior axillary line could be heard a peculiar, harsh clicking sound, synchronous with systole, which resembled pebbles dropped in a metal bucket. The patient himself listened to the sound and avowed it was the same as that he heard the night before. The heart sounds proper were somewhat faint but otherwise normal in quality, and there was no evidence of cyanosis, venous engorgement or mediastinal shift.

Laboratory studies on admission showed a white count of 8,800 with a normal differential count. Subsequent hematologic studies were well within normal limits. X-ray and fluoroscopy of the chest made twelve hours after onset of the present illness revealed a large area of pneumothorax on the left, principally affecting the upper lobe which was almost entirely collapsed. There was no displacement of the mediastinum nor was air visualized within that structure.

Bed rest, sedation and occasional doses of pantopon constituted the only measures instituted for therapy. Second strength PPD, injected intracutaneously, showed a weakly positive reaction. Sedimentation rate was normal.

Except for rather severe, right lower quadrant pain for two or three days following hospital admission, the patient pursued an uneventful course. On the eleventh day x-ray showed virtually complete re-expansion of the left lung. The patient was discharged on the fourteenth day without specific recommendations other than to keep the glottis open at all times, especially when any strenuous exertion was undertaken.

Definition. For the purposes of this paper spontaneous is taken to mean arising without apparent cause in presumably healthy individuals in whom no underlying pathologic condition is subsequently demonstrated. Although emphysema has been defined as "the presence of air in the interstices of the connective tissue of a part,"[16] its use in the present context, mediastinal emphysema, has been to indicate the presence of free air in the mediastinum. Pneumothorax,[17] after Taschman, represents the condition in which air is present in the pleural cavity.

Rather rigid definitions have been adopted in the hope that subsequent confusion will be avoided. Spontaneous mediastinal emphysema, for example, has been described in patients undergoing labor,[18] in the newborn[19] and in asthmatics[20] while spontaneous pneumothorax, of course, has been observed in many infectious processes of the lungs[21] as well as in congenital cystic disease,[22] bronchiectasis[23] and even malignancy.[24] The present report does not include such cases.

Incidence. The incidence of spontaneous mediastinal emphysema is difficult to calculate in that only forty-two cases, including the one presented here, have been reported.[1–15,25–34] Hamman stated as far back as 1939,[3] however, that more and more physicians had reported to him personally concerning recognition of the condition. It is probable then that the condition is much more common than figures based upon the literature would indicate.

Spontaneous pneumothorax appears to be far more prevalent. Blackford[35] found fifteen cases in three years in Virginia college students while Wilson[36] found eleven in a four-year period at Yale. Schneider,[37] at the induction station in Grand Central Terminal, states that 1/500 of the inductees gave a verifiable history of pneumothorax. An estimate of 1–1,000 in the young adult male population would probably not be far wrong.

Age. Both spontaneous mediastinal emphysema and spontaneous pneumothorax are notably confined to young people. Inasmuch as a summary of the cases of the former condition has not thus far appeared in the literature, the author has charted them in detail with respect to age, a policy followed in other matters pertaining to mediastinal emphysema. (Table I.)

A breakdown of the 199 cases of spontaneous pneumothorax reported by Ornstein,[21] Wilson,[36] Schneider,[37] Blackford,[35] Leggett[38] and Goldman[39] reveals that 94 per cent of the patients were between the ages of fifteen and forty years.

Sex. The male sex is predominantly favored by both diseases. Using the same sources for our figures as for age, we find only two females with spontaneous mediastinal emphysema and three with pneumothorax.

History of Effort. In Table I the judgment as to whether or not the patient had undergone "none to slight" exertion was somewhat difficult. Any customary activity not commonly regarded as strenuous was termed slight, such as walking home from work,[3] driving a car[3] or even servicing a mortar.[15] Of the five cases listed as those performing moderate to severe exertions, running one-half a mile,[25] cycling,[25] performing military calisthenics,[15] swimming[15] and, perhaps unfairly in the case of a seventeen year old girl, dribbling a basketball[5] were included.

According to Ornstein,[21] only 22 per cent of his patients gave a history of exertion while Schneider[37] reported such a history in 30 per cent. In twenty-three of thirty-nine cases (59 per cent) completely reported by Cohen and Kinsman[40] there was no provoking cause; ten soldiers (26 per cent) had undergone mild exertion, such as walking. At all events, if these cases (186) are representative a history of exertion in spontaneous pneumothorax is present in less than one-third of the cases.

ETIOLOGY

Pulmonary tuberculosis was long considered the chief causal factor in the large majority of cases of spontaneous pneumothorax. Biach,[23] who is representative of the older writers on the subject, gave an estimate of 80 per cent. After the report, in 1932, of Kjaergaard,[22] who found tuberculosis in only one of forty-nine cases, a flood of contrary estimates was released. Perry[41] found tuberculosis in 6 of 250 cases; Ornstein,[21] in three of fifty-eight, and Schneider,[37] in one definitely and two problematically of one hundred cases—an overall incidence of 3 per cent in 470 cases. Active pulmonary tuberculosis was observed in two (5 per cent) of the cases reported by Cohen and Kinsman.[40] In addition to the clinical statistics militating against the culpability of tuberculosis in spontaneous pneumothorax, Hamman[42] provides further negative evidence in the pertinent observation that pneumothorax

TABLE I
SPONTANEOUS MEDIASTINAL EMPHYSEMA

Age (in yr.)	Cases	Per Cent
15–19	6	14
20–29	26	62
30–39	5	12
40–49	1	2
50–59	2	5
* Unlisted	2	5
Total	42	100

Sex	Cases	Per Cent
Male	40	95
Female	2	5
Total	42	100

Exertion	Cases	Per Cent
None to slight	37	88
Moderate to severe	5	12
Total	42	100

* Medical student;[4] lawyer.[23]

in tuberculous patients is a dramatic event attended by a violent reaction of the pleura and definite constitutional symptoms. When such is not the case, pursues Hamman, pneumothorax must be regarded as due to the same mechanism as in the healthy. Last, tuberculosis has not been found in the few postmortems done in clinical cases of spontaneous pneumothorax.

Although uncommon, spontaneous pneumothorax has been known to occur in congenital cystic disease of the lung,[22] in bronchial asthma,[43] bronchiectasis,[23] and even malignancy.[24] Such conditions, however, hardly meet our criterion of "spontaneous," absence of demonstrable underlying pathology.

Ornstein[21] has advanced a rational and widely accepted explanation of pneumothorax. The time-honored theory of "ruptured emphysematous bleb" had not been well supported by postmortem evidence, nor had cases of pneumothorax been observed in those, especially the elderly, who suffered from emphysema. Why, wondered Ornstein, did spontaneous pneumothorax occur almost exclusively in healthy young males? Why, again, was there so seldom a history of effort in these patients? Under the fluoroscope Ornstein observed that the apices of the lungs could be seen to "light up" when in full inspiration the glottis is closed and the thoracic and abdominal muscles compressed, just the condition during coughing or strenuous effort. Air is driven from the lung bases to the apices which become markedly distended. This forceful inflation, reasoned Ornstein, could easily overdistend and rupture the elastic fibers of the subpleural alveoli, especially at the apex. The result would be the formation of a subpleural bleb. If, by some such mechanism as a check valve which would admit air to the bleb but prevent its egress, the bleb grew increasingly distended, eventual rupture would occur with the patient at rest. A check valve of the sort envisaged has actually been observed by Kjaergaard.[22] The first mechanism thus outlined would explain the incidence in healthy young males who are usually given to severe exertions. The second goes far to explain why pneumothorax so often occurs when the patient is at rest. Since circumstances favorable for study are very seldom obtained so rarely does death ensue, any etiologic concept must remain largely theoretical. Ornstein's appears to be the best of the present explanations.

The pathologic physiology of spontaneous mediastinal emphysema is similar and possibly related to that of pneumothorax. Macklin[44] has shown experimentally in cats and rabbits that when air under a pressure of from 1 to 22 mm. Hg is forced through a truncated catheter introduced into the right lower lobe bronchus, distention and rupture of the alveoli follow. The air thus released into the pulmonary interstitial tissue dissects along the sheaths of the pulmonary vessels to the lung roots. The pressure gradient from the alveolus to the vascular sheath is said to be the direct result of overdistention which pulls away the enveloping alveolus from the vessel sheath.[45] Once at the lung roots the air forms large blebs in the sheaths of the pulmonary vessels. When the pressure is great enough, the air ruptures into the mediastinum. Still greater pressure results in pneumothorax and subcutaneous or retroperitoneal emphysema, respectively. In the animals showing Hamman's sign bubbles of air were observed between the anterior pericardium and thoracic cage. Careful examination of those cases with pneumothorax disclosed no evidence of a tear in the visceral pleura of the lungs. In many cases, however, rents in the thin mediastinal wall were observed.

Hamman[42] believes that Macklin's experimental findings obtain in human cases of spontaneous mediastinal emphysema, the sequence of events being first rupture of the alveoli lying on interstitial bands of connective tissue, then entrance of the air into interstitial tissues and dissection along the sheaths of the pulmonary vessels where it escapes into the mediastinum. Free air in the mediastinum is gradually absorbed although why it is confined there is not

fully understood. A great amount of air will escape because of pressure, usually into the pleura. In exceptional cases subcutaneous or retroperitoneal emphysema result.

To go further Hamman postulates that many cases of spontaneous pneumothorax might arise from the same cause. Macklin's failure to find tears in the visceral pleura of his experimental animals is cited as evidence. Again, pneumothorax and mediastinal emphysema are often found in association. A review of the forty-two spontaneous cases of mediastinal emphysema reveals associated pneumothorax in 55 per cent of the cases. While this incidence is high enough to be suggestive, two points must not be overlooked. First, mediastinal emphysema has not been observed in the vast majority of cases of spontaneous pneumothorax. Second, in all the cases in which the two conditions were associated the pneumothorax was on the left side. The reports on spontaneous pneumothorax show that the accident is equally common on the right. Of Schneider's one hundred cases, for example, fifty-five were right-sided, forty-four left-sided and one was bilateral[37] while Cohen and Kinsman[40] report 54 per cent of their cases as right-sided and 46 per cent left-sided. Although as Hamman testifies there is no theoretical reason why the pneumothorax in cases of mediastinal emphysema should be on the left, the fact that in all reported cases the lesion has been left-sided cannot be lightly dismissed. The middle way is taken by McGuire and Bean[5] who state that in interstitial emphysema of the lungs resulting from a rupture of alveoli, the air may travel along interstitial bands toward the hilum and enter the mediastinum or else, more commonly, it might pass outward directly to the pleura where it forms a bleb. The latter eventuality, while it is at variance with the pressure gradients observed by Macklin, closely parallels the theory of Ornstein. At all events the theories propounded to explain the pathogenesis of spontaneous mediastinal emphysema and spontaneous pneumothorax are closely allied.

SIGNS AND SYMPTOMS

Pain is the chief complaint in nearly all cases of spontaneous mediastinal emphysema. (Table II.) In the two cases[32,34] in which pain was absent the first manifestations were emphysema of the scrotum and pneumoperitoneum but these were not truly uncomplicated cases. Usually severe, sharp and stabbing, the pain begins in the precordial and substernal region and radiates through to the back, up into the left shoulder and side of the neck and, at times, down the left arm.[4] Changes of position, coughing or even swallowing tend to accentuate the pain.[3] It lasts as a rule for many hours before diminishing in severity. At times the pain may begin in the left side of the chest before shifting to the substernal region. In such instances interstitial emphysema of the lungs precedes pneumomediastinum.[45]

TABLE II
SPONTANEOUS MEDIASTINAL EMPHYSEMA—ANALYSIS OF FORTY-TWO CASES

Symptoms	No. Cases	Per Cent
1. Chest pain	40	95
2. Dyspnea	12	29

Signs	No. Cases	Per Cent
1. Peculiar sound over heart	38	90
2. Diminution of cardiac dullness	14	33
3. Absence of constitutional symptoms	38	90
4. Subcutaneous emphysema	10	24

X-ray Findings	No. Cases	Per Cent
1. Air in mediastinum	16	38
2. Pneumothorax	23	55

The chief associated symptom is dyspnea which has been recorded in twenty-nine instances. Owing to accentuation of the pain by respiration, some degree of dyspnea may result from mere "splinting" of thoracic movement. In some cases, however, enough air may be trapped in the mediastinum to cause embarrassment to the vital structures therein. Should this state become pronounced, with venous engorgement, cyanosis and circulatory collapse, immediate and heroic measures must be undertaken for relief. Such have not been necessary in the spontaneous cases thus far reported.

Onset of spontaneous pneumothorax as a rule is characterized by sudden, sharp, severe pain localized over the affected lung which may extend to the shoulder, neck, back and even the abdomen.[17,40] The author has seen one case which simulated an acute abdominal catastrophe. Changes of position and deep respiration markedly accentuate the pain. Even riding in a car might make the pain almost unbearable. A small minority of patients, however, may be unaware of the condition which has been discovered by Schneider,[37] Wilson[36] and Blackford[35] upon routine x-ray. Duration of the pain, as in mediastinal emphysema, is a matter of hours. Some measure of relief is obtained by bed rest.

Dyspnea and cyanosis are often observed in spontaneous pneumothorax, their severity being in rough proportion to the degree of collapse of the affected lung. They arise, according to Ornstein,[21] from three causes: immobilization of the thorax from pain, poor aeration of the venous blood in the collapsed lung, the circulation of which becomes negligible after the first twenty-four hours, and actual loss of vital capacity due to pneumothorax. When seen immediately after onset, these patients may show signs of shock, with pallor, sweating, rapid pulse rate and decline in blood pressure. A slight reflex cough is commonly observed in the early stages.[17,21] Should any of these associated symptoms be pronounced one must suspect tension pneumothorax and take appropriate measures for immediate relief.

The most distinctive clinical sign in mediastinal emphysema is the peculiar sound heard over the heart. (Table II.) Known as Hamman's sign[3] it has been described as a "crunching, crackling, clicking, bubbling or churning noise" synchronous with the heart beat. Other authors have added colorful descriptions, including the "rattle of dried peas on taut canvas,"[25] "the wrinkling of a newspaper"[5] and "the grinding of gears."[11] Whatever the descriptive phrase chosen by the individual writer, all agree that once heard the sound is never forgotten. It cannot, as Stein[13] emphasizes, be confused with any other condition nor does it occur in any other condition. Adcock[32] has heard in four patients shortly after induction of artificial pneumothorax a very loud, single, slapping sound synchronous with systole but usually audible only in one phase of respiration with the patient lying on the left side. In mediastinal emphysema, by contrast, one hears a crackling and crunching throughout the respiratory cycle. Greene[31] writes that a knocking, tapping or metallic sound may accompany left pneumothorax but that bubbling, crunching or clicking noises indicate emphysema of the pulmonary interstitial tissues or the mediastinum. In late or transitional stages, however, as Miller[15] warns the sound may resemble a rough pericardial friction rub. Of interest and distinct help in diagnosis is the fact that of the thirty-eight patients in whom Hamman's sign was detected twenty-one, or 55 per cent, heard the sound themselves.

Diminution or obliteration of cardiac dullness upon percussion has been reported in about one-third of the cases of mediastinal emphysema. (Table II.) When present this is a virtually pathognomonic sign.

Absence of constitutional symptoms provides negative evidence of inestimable value in differentiating mediastinal emphysema from more serious disorders, such as myocardial infarction, pericarditis, pulmonary

embolism and dissecting aneurysm of the aorta.[13,15] In only four cases has fever of over 100°F. been reported; at least three of these had complicating disorders.[3,32,34] Systemic manifestations, such as tachycardia, fall in blood pressure, leukocytosis or increased sedimentation rate do not occur.

Subcutaneous emphysema of the neck or outer chest wall, detected by observation of swelling and crackling to the touch in these tissues, affords conclusive evidence of mediastinal emphysema.[3] It has been reported, however, in only one-fourth of the cases.

The signs of spontaneous pneumothorax may be summarized as follows:[36] respiratory lag on the affected side; slight increase in resonance over the affected area; diminished to absent breath sounds and vocal or tactile fremitus and, possibly, displacement of the mediastinum away from the affected side. Inasmuch as they are just what we should expect in view of the underlying pathologic condition, these signs do not require much discussion. It is worthy of emphasis, however, that diagnosis of pneumothorax by physical signs alone is many times exceedingly difficult. The air might represent but a thin sheet interposed between the lung and chest wall, in which event slight dullness instead of hyperresonance results. Tympany, although mentioned in most of the textbooks, is, as Wilson says,[36] seldom observed. Air under pressure is more likely to give a wooden or flat note to percussion. The coin sound and succession splash do not occur in uncomplicated pneumothorax.

X-ray Findings. Air within the mediastinum has been roentgenographically demonstrated in 38 per cent of the reported cases of spontaneous mediastinal emphysema. In the anteroposterior view the characteristic finding is a thin line of density parallel to the border of the heart, usually the left border.[3] Lateral views may show air pocketed between the anterior border of the heart and the chest wall. Oblique views are valuable in revealing air in the posterior mediastinum. All three views should be taken in cases of suspected mediastinal emphysema. Positive x-rays afford incontrovertible proof of the diagnosis.

A review of the cases of spontaneous mediastinal emphysema shows that in twenty-three cases, 55 per cent, left pneumothorax was present upon x-ray. Although usually small[33] and confined to the apical portion, the area of pneumothorax may be large, causing 40 to 75 per cent collapse of the affected lung.[15]

The outstanding finding in spontaneous pneumothorax is, of course, presence of air in the pleural cavity. Wilson[36] as well as Greenberg[46] emphasizes that air may be missed in mild cases unless a film is taken at expiration. Rarely will a lateral film show pneumothorax in those patients in whom the collapsed lung is plastered against the posterior wall of the pleural cavity. Fluoroscopy alone, as Blackford warns,[35] is not a reliable method of demonstrating pneumothorax. Atelectasis is always present to some degree, usually involving the upper lobe of the affected lung. According to Taschman,[17] a large degree of collapse is the general rule but Ornstein[21] reports forty-one of his fifty-eight cases (70 per cent) as "slight." Displacement of the mediastinum, heart, great vessels and trachea may be observed in pronounced cases.

A small amount of fluid is observed in the costophrenic sinus in about one-half of the patients with spontaneous pneumothorax.[21] Any measurable quantity of fluid should arouse strong suspicions of tuberculosis or, much more rarely, of hemopneumothorax.

Adhesions are rarely observed in spontaneous pneumothorax.[17,21] Of the five patients showing adhesions observed by Cohen and Kinsman[40] one had active and two had inactive tuberculosis. Their presence leads one to suspect tuberculosis.

Diagnosis. "Any diagnosis is easy," the late Soma Weiss used to say, "if you can think of it"! Sudden onset of severe chest pain in a previously healthy young male should always bring to mind the possibility of spontaneous pneumothorax or mediastinal emphysema. Careful examination

of the patient will nearly always, in the latter case, disclose the peculiar sound over the heart often accompanied by diminution of cardiac dullness. In the former, efforts should be made to elicit presence of air in the pleural cavities. Whenever possible, x-ray should be taken to provide confirmatory evidence.

The striking absence of constitutional symptoms in the two disorders makes the exclusion of more serious disorders relatively easy and certain. Myocardial infarction, pericarditis, pulmonary embolism, dissecting aneurysm of the aorta and acute abdominal catastrophes are rarely unaccompanied by fever, disturbances of pulse rate or blood pressure, leukocytosis or elevated sedimentation rate. Although many small pneumothoraces are doubtless misdiagnosed as pleurisy, intercostal neuralgia, muscle strain and the like,[35] such errors can be avoided by careful physical examination and more liberal use of roentgenography.

Tuberculosis must be ruled out in patients with spontaneous pneumothorax. Reliance upon statistics alone, although reassuring, is indefensible when one is dealing with an individual case. Here again the absence of constitutional symptoms is of prime importance. The presence by x-ray of adhesions or more than a small quantity of fluid puts the burden of proof upon him who says tuberculosis is not present; prolonged observation with frequent sputum examinations and cultures, including those from gastric washings, should be carried out in such cases. Even in adults the tuberculin test has proved valuable; when it is negative, the odds are strongly against tuberculous infection.[38,47]

TREATMENT

Treatment of both spontaneous mediastinal emphysema and spontaneous pneumothorax is, in all but rare cases, "masterful inactivity."[48] Bed rest and sedation together with opiates suffice for those with severe cases. Cohen and Kinsman[40] advocate the use of oxygen for severe dyspnea. The length of time that a patient should remain in bed is still being debated. Those who specialize in tuberculosis advise at least four weeks' bed rest;[17,21] others, such as Blackford[35] and Perry,[41] believe two weeks to be enough. Since re-expansion of the lungs takes place in most cases within two weeks and since the patients affected are healthy young males, the shorter period would seem sufficient.

Amounts of air large enough to cause circulatory or respiratory embarrassment should be aspirated. In the case of mediastinal emphysema this operation may be performed either by insertion of a hollow curved needle into the mediastinum or, especially when subcutaneous emphysema of the neck is present, by incision through the jugulum.[33] Such contingencies have not arisen in the reported cases of spontaneous mediastinal emphysema. Pneumothorax of the "tension" type is aspirated by use of the conventional apparatus for giving artificial pneumothorax, with the bottles reversed, by attaching flexible tubing to the chest needle and submerging the other end in a jar of water or even by use of a simple needle and syringe outfit.[17] It must be emphasized, however, that the collapsed lung in spontaneous pneumothorax is in the ideal condition for repair. Drawing off air during the first three days after onset serves only to increase the size of the hole in the visceral pleura, with resultant delay in recovery.[36] Even in tension pneumothorax Hennell and Steinberg[49] advise avoidance of aspiration; the patient is given sedatives and instructed to lie on the affected side. In patients with bilateral pneumothorax great judgment must be exercised in the performance of aspiration in order to maintain a balance between the two sides. The needles should, according to Taschman,[17] be left in some time.

In the uncommon but ominous complication of hemopneumothorax the blood must be aspirated and partially replaced by air lest further bleeding be encouraged.[39] One must insist on rigid enforcement of bed rest.

Prognosis. When life is concerned, the prognosis either of mediastinal emphysema

or of pneumothorax, when spontaneous in origin, is excellent. Although the rare bilateral pneumothorax is said to carry a mortality rate approaching 50 per cent[35] and hemopneumothorax to cause fatalities in from 16 to 37 per cent of reported cases,[35,36] those with uncomplicated cases invariably recover. Emphasis must be placed on complete recovery for many patients can thereby be spared undue alarm and unnecessary anxiety. There is a word of caution to be said: Pneumothorax is recurrent in about 25 per cent of the cases;[21,36,37,40,49] eleven patients of the forty-two reported cases of mediastinal emphysema (26 per cent) have suffered recurrences.[4,7,9,13–15,25,30,33] Five patients (12 per cent) suffered pneumothorax as distinct from that observed in association with mediastinal emphysema.[3,4,7,33] The patient should be informed then that there is a definite likelihood of recurrence yet there is small need for anxiety on that score. After the age of thirty recurrences are exceedingly rare. Kjaergaard[22] and later Hennell and Steinberg[49] have successfully treated patients with multiple recurrences by inducing, by means of sclerosing solutions, a sterile pleuritis. Such a procedure, however, is seldom indicated.

SUMMARY AND CONCLUSIONS

A case of spontaneous mediastinal emphysema with left pneumothorax is presented.

Spontaneous mediastinal emphysema and spontaneous pneumothorax are benign disorders which predominantly affect young men. Theories regarding the etiology of the two conditions are closely allied. Both are chiefly characterized by sudden onset of severe pain in the chest in the previously healthy. Careful examination of the chest, supported by roentgenographic studies, will nearly always reveal the diagnosis. Valuable confirmatory evidence is afforded by failure to detect signs of a systemic disturbance.

Therapy is principally supportive although aspiration of trapped air may be indicated in those with severe cases. While recurrences are common, the prognosis in uncomplicated cases is uniformly good.

REFERENCES

1. Lister, W. A. Case of pericardial knock associated with spontaneous pneumothorax. *Lancet*, 1: 1225–1226, 1928.
2. Wolferth, C. C. and Wood, F. C. Angina pectoris. *M. Clin. North America*, 13: 947–967, 1930.
3. Hamman, L. Spontaneous mediastinal emphysema (Henry Sewall Lecture). *Bull. Johns Hopkins Hosp.*, 64: 1–21, 1939.
4. Morey, J. B. and Sosman, M. C. Spontaneous mediastinal emphysema, with report of case associated with spontaneous pneumothorax. *Radiology*, 32: 19–22, 1939.
5. McGuire, J. and Bean, W. B. Spontaneous interstitial emphysema of lungs. *Am. J. M. Sc.*, 197: 502–509, 1939.
6. Wolff, B. P. Spontaneous interstitial emphysema of the lungs; report of an additional case. *Ann. Int. Med.*, 13: 1250–1253, 1940.
7. Pinckney, M. M. Mediastinal emphysema and idiopathic spontaneous pneumothorax. *Virginia M. Monthly*, 68: 315–319, 1941.
8. Matthews, E. Spontaneous mediastinal emphysema. *New Orleans M. & S. J.*, 93: 523–524, 1941.
9. Griffin, R. J. Spontaneous pneumothorax. *Kentucky M. J.*, 39: 284–288, 1941.
10. Miller, J. Spontaneous interstitial emphysema of lungs; report of 2 cases and summary of literature. *Ohio State M. J.*, 37: 1056–1059, 1941.
11. Lintz, R. M. Spontaneous mediastinal emphysema. *Arch. Int. Med.*, 71: 256–261, 1943.
12. Miller, H. Spontaneous mediastinal emphysema. *Ann. Int. Med.*, 21: 998–1010, 1944.
13. Stein, M. H. Spontaneous mediastinal emphysema. *New York State J. Med.*, 45: 1659–1662, 1945.
14. Styron, C. W. Spontaneous mediastinal emphysema. *New England J. Med.*, 225: 908–909, 1945.
15. Miller, H. Spontaneous mediastinal emphysema with pneumothorax simulating organic heart disease. *Am. J. M. Sc.*, 209: 211–220, 1945.
16. Stedman's Shorter Medical Dictionary. Chicago, 1943. Wilcox & Follett Co.
17. Taschman, M. Spontaneous pneumothorax. *J. Mt. Siani Hosp.*, 10: 684–697, 1944.
18. Faust, R. C. Subcutaneous emphysema during labor. *Northwest Med.*, 39: 24–26, 1940.
19. Gumbiner, B. and Cutler, M. M. Spontaneous pneumomediastinum in newborn. *J. A. M. A.*, 117: 2050–2054, 1941.
20. Rosenberg, L. and Rosenberg, J. Subcutaneous emphysema complicating bronchial asthma; report of case and analysis of 17 previously reported cases. *Am. J. M. Sc.*, 195: 682–685, 1938.
21. Ornstein, G. G. and Lercher, L. Spontaneous pneumothorax in apparently healthy individuals; clinical study of 58 cases with discussion of pathogenesis. *Quart. Bull., Sea View Hosp.*, 7: 149–187, 1942.
22. Kjaergaard, H. Spontaneous pneumothorax in apparently healthy. *Acta med. Scandinav.*, 43: 1–159, 1–93, 1932.

23. Biach, Alois. Zur Etiologie des Pneumothorax. *Wien. med. Wchnschr.*, 30: 6, 1880.
24. Tuggle, Allan. Personal communication.
25. Scott, A. M. Significance of anginal syndrome in acute spontaneous pneumomediastinum. *Lancet*, 1: 1327–1330, 1937.
26. Caldwell, H. W. Spontaneous mediastinal emphysema. *J. A. M. A.*, 116: 301–302, 1941.
27. Murphy, J. P. and Zeis, L. B. Spontaneous interstitial mediastinal emphysema; report of case. *J. Missouri M. A.*, 39: 5–7, 1942.
28. Kellogg, D. S. Spontaneous pneumomediastinum (mediastinal emphysema). *Am. J. Roentgenol.*, 48: 510–512, 1942.
29. Meek, E. M. Spontaneous mediastinal emphysema; summary and report of case. *South. M. J.*, 35: 990–992, 1942.
30. Munroe, D. S. and Webb, G. A. C. Spontaneous mediastinal emphysema. *Canad. M. A. J.*, 48: 145–148, 1943.
31. Greene, J. A. Unusual sounds emanating from the chest; cause and diagnostic significance of bubbling, clicking, crunching, knocking, and tapping sounds, with report of 2 cases in interstitial emphysema of lung and mediastinum. *Arch. Int. Med.*, 71: 410–414, 1943.
32. Adcock, J. D. Spontaneous interstitial emphysema of lung, with mediastinal, retroperitoneal and subcutaneous emphysema. *Arch. Int. Med.*, 71: 650–657, 1943.
33. Hamman, L. Frank Billings Lecture. *J. A. M. A.*, 128: 1–6, 1945.
34. Lefkovits, A. M. and Schlessinger, H. L. Electrocardiographic changes in case of spontaneous mediastinal and subcutaneous emphysema; case report. *Clinics*, 4: 863–866, 1945.
35. Blackford, S. D. Spontaneous pneumothorax in college students. *J. A. M. A.*, 113: 737–739, 1939.
36. Wilson, J. L. Spontaneous pneumothorax. *Internat. Clin.*, 1: 157–175, 1937.
37. Schneider, L. and Reissman, I. I. Idiopathic spontaneous pneumothorax; history of 100 unselected cases. *Radiology*, 44: 485–488, 1945.
38. Leggett, E. A., Myers, J. A. and Levine, I. Spontaneous pneumothorax; report of 31 cases. *Am. Rev. Tuberc.*, 29: 348–361, 1934.
39. Goldman, A. and Roth, H. Spontaneous pneumothorax; report of 3 unusual cases. *Ann. Int. Med.*, 21: 1011–1021, 1944.
40. Cohen, S. and Kinsman, J. M. Nontraumatic spontaneous pneumothorax among military personnel. *New England J. Med.*, 235: 461–467, 1946.
41. Perry, K. M. A. On spontaneous pneumothorax. *Quart. J. Med.*, 8: 1–21, 1939.
42. Hamman, L. A note on the mechanism of spontaneous pneumothorax. *Ann. Int. Med.*, 13: 923–928, 1939.
43. Derbes, V. J., Engelhardt, H. T. and Soderman, W. A. Unusual complications of bronchial asthma; air in extra-pulmonary spaces. *Ann. Allergy*, 3: 21–26, 1945.
44. Macklin, C. C. and Macklin, M. C. Essays in Biology in Honor of Herbert M. Evans. P. 331. Los Angeles, 1943. University of California Press.
45. Macklin, C. C. Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum; clinical implications. *Arch. Int. Med.*, 64: 913–926, 1939.
46. Greenberg, S. Superior value of expiratory roentgenogram in diagnosis of incomplete pneumothorax. *Am. J. Roentgenol.*, 32: 330–332, 1934.
47. Ylvisaker, L. S., Kiessling, C. E. and Kirkland, H. B. Nontuberculous spontaneous pneumothorax. *Am. Rev. Tuberc.*, 41: 114–116, 1940.
48. Meakins, J. C. The Practice of Medicine. 3rd ed., p. 487. St. Louis, 1940. C. V. Mosby Company.
49. Hennell, H. and Steinberg, M. F. Tense pneumothorax; treatment of chronic and recurrent forms by induction of chemical pleuritis. *Arch. Int. Med.*, 63: 648–663, 1939.

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Pyoderma Gangrenosum in Chronic Non-specific Ulcerative Colitis*

A Report of Three Cases

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DERMATOLOGIC complications are not uncommon in patients with non-specific ulcerative colitis. The incidence varies from 2.45 per cent in Bargen's[1] series to 10.7 per cent in the group reported by Ricketts and Palmer.[2] Among the cutaneous manifestations the pyogenic lesions are particularly important because of their marked resistance to treatment and the prolonged disability of the patient. Pyoderma gangrenosum represents the most severe of the cutaneous suppurative complications. This condition is characterized by pustular lesions which tend to break down, to ulcerate and to extend in all directions. The ulcers discharge foul smelling, purulent material. They may be so extensive as to result in massive necrosis of large portions of the integument. A variety of bacteria, especially staphylococci, streptococci, Bacillus pyocyaneus, B. necrophorum and B. coli, have been cultured from the lesions. The ulcerations typically are resistant to almost all forms of therapy. Healing proceeds slowly and with residual atrophic scarring. Any portion of the skin may be involved; however, involvement of the face apparently is rare.

Pyoderma gangrenosum occurs usually as a complication of chronic debilitating illnesses, and its development seems to be related to the poor nutritional state of the patient and his decreased resistance to infection. Of the five cases described by Brunsting, Goeckerman and O'Leary[3] four had chronic non-specific ulcerative colitis while the fifth patient had empyema. Jankelson and Marshall,[7] Lane,[4] Cohen,[5] Cowet,[6] Jankelson and Massell,[7] Jankelson and McClure,[8] Mintzer[9] and Brooke[10] also have reported pyoderma gangrenosum as a complication of non-specific ulcerative colitis. Felsen[10,11] has recorded its appearance in patients with bacillary dysentery.

The purpose of this paper is to indicate the importance of pyoderma gangrenosum as a complication in three patients with chronic non-specific ulcerative colitis. In Case 1 the pyoderma was so severe and resistant to therapy that it assumed primary significance in the prolonged disability of the patient.

CASE REPORTS

CASE 1. M. R., No. 97682, a forty-seven year old housewife was first seen in January, 1934. She had been troubled with "constipation" for many years, but also had experienced episodes of diarrhea following excessive ingestion of fresh fruits and vegetables. Diarrhea recurred two weeks before admission, with the daily passage of as many as fifteen to thirty loose stools containing mucus and blood. There was marked rectal tenesmus with abdominal cramps and distention. There had been a weight loss of 10 pounds. No significant abnormalities were detected on physical examination. Proctoscopic examination revealed numerous small ulcerations and bleeding points of the rectal mucosa. Routine laboratory studies were normal; the Wassermann test was negative. Examination of one stool specimen was negative for Endameba histolytica. Roentgen examination of the colon

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demonstrated a marked irritability of the bowel and an absence of haustral markings. A diagnosis was made of non-specific ulcerative colitis and the patient was treated with a bland, low residue diet, antispasmodics and rest. She made excellent progress during the next seventeen months and gained 13 pounds in weight. In May, 1935 the diarrhea recurred after the patient had taken Ex-lax for relief of constipation. She lost 8 pounds in two weeks. Proctoscopy revealed a granular, friable mucosa. Therapy was resumed but the patient was not seen again until January, 1945, eleven years after the initial examination.

She had enjoyed fairly good health until 1939, at which time the diarrhea had recurred and had persisted intermittently until July, 1943. Since that time the bowels apparently moved normally. The patient had been receiving injections of liver and iron and after one such treatment she experienced a sense of numbness at the site of injection on the exterior side of the right upper arm, followed by pain, redness and swelling of the area. A similar lesion soon appeared on the right leg. These became necrotic and ulcerated. Many boils subsequently appeared on the skin in various parts of the body; these lesions ulcerated and healed slowly, with residual scarring. The two original ulcerations, however, did not heal. In February, 1944 the patient was hospitalized elsewhere because of the ulcerations of the skin. Diagnoses were made of chronic ulcerative colitis and pyoderma gangrenosum. Therapy included twelve blood transfusions and 800,000 units of penicillin given intramuscularly; 20 per cent sulfathiazole in glucose was applied to the ulcerations. Definite improvement resulted although the lesions were not completely healed at the time the patient was discharged from the hospital.

In April, 1944 the patient sought relief at a second hospital because of the persistent and distressing cutaneous ulcerations. Hemolytic streptococci were isolated from cultures of the lesions. The lesions temporarily improved after each of four blood transfusions. Administration of 500,000 units of penicillin intramuscularly and 100 cc. of antistreptococcus serum intravenously, and 10 per cent sulfanilamide and 10 per cent sulfathiazole ointment applied locally were ineffective. The patient also received a high caloric diet, large amounts of vitamins A and C and such proprietary preparations as lextron ferrous, aminoids and cortinoral. The local application of 10 per cent sulfanilamide and allantoin in a water-soluble base apparently exerted a beneficial effect temporarily. Skin grafting of the ulcerated areas was attempted in October, 1944 but these efforts were not successful. At the conclusion of this program of treatment the lesions on the right arm and right leg were not healed although definite improvement had occurred.

However, two months prior to the patient's admission to the Albert Merrit Billings Hospital in January, 1945 the ulcerations enlarged, bled easily, were painful and seriously interfered with movements of the right shoulder, elbow and leg. Pain in the back and both lower extremities at times was so marked as to require the use of codeine. Physical examination revealed an undernourished, chronically ill female. The significant findings were confined to the skin. Numerous fibrotic scars were present on the face, abdomen and inguinal regions and over both thighs. An enormous ulceration extended around the lower half of the right upper extremity and antecubital region; the base of the lesion consisted of poorly vascularized granulation tissue, partially covered with purulent exudate. Small red papules and pustules were located around the borders of the ulcerations. A similar gigantic lesion involved the lower half of the right leg. Smaller, more superficial ulcerations were present behind each ear. The erythrocyte count was 4.05 million, the hemoglobin 12.0 Gm. and the leukocyte count 9,800; the differential blood smear was normal. The Wassermann test was negative. Three urine specimens were normal. The plasma proteins measured 7.08 Gm. per cent. Six stool specimens were negative for E. histolytica and pathogenic bacteria. Detailed bacteriologic studies including aerobic and anaerobic cultures were made; B. pyocyaneus and Staph. aureus were isolated in several cultures. Careful repeated search for E. histolytica, various types of fungi and acid-fast organisms, including inoculation of the exudate into a guinea pig, were completely negative. A diagnosis of pyoderma gangrenosum was made. Various types of therapy were employed locally in an effort to stimulate healing of the cutaneous lesions. Five and 10 per cent ammoniated mercury and moist applications of penicillin in a concentration of 200 units per cc. were ineffective. Ultraviolet light was applied daily to the entire body and locally to each

FIG. 1. Case I. Extensive necrotizing pyoderma of the right upper extremity.

lesion. The patient's temperature remained moderately elevated, with peaks up to 38.5°C. A subcutaneous abscess, located over the right first rib, required surgical drainage. After six weeks wet dressings of silver nitrate solution, in a concentration of 1:10,000, were applied daily and 5 per cent silver nitrate was applied to the surfaces of the ulcerations after each change of a dressing. A distinct tendency to healing was observed several days after this therapy was instituted. Improvement continued but healing proceeded at an extremely slow rate. The patient also received vitamins, liver and iron and one transfusion of 600 cc. of whole blood. The lesions became less painful. The temperature gradually returned to normal and after two and one-half months of hospitalization the general condition of the patient improved sufficiently to enable her to continue treatment at home. It is of interest to note that no disturbance in bowel function occurred during this period; an average of one normal stool was passed daily.

Improvement of the cutaneous lesions was temporary, however, and the patient was readmitted to the hospital in April, 1945 because of an increase in the size and sensitivity of the ulcerations. These now involved the entire right arm from the shoulder to the elbow (Fig. 1) and the right leg from just below the knee to the ankle. (Fig. 2.) The base consisted in part of granulation tissue and in part of black necrotic masses covered with foul smelling, green purulent exudate. (Figs. 3 and 4.) Routine laboratory studies again were negative except

FIG. 2. Case I. Lesions involving the right leg with extensive ulcerations and purulent exudate.

for a mild secondary anemia. Therapy, with ultraviolet light and local applications of silver nitrate, 1:10,000 sol, was resumed. The lesions improved slowly but definitely. After three weeks of treatment the condition of the patient was considered to be better than at any previous stage of her illness. At this time she became much disturbed by a difficult family situation and was obliged to leave the hospital against advice. She has not returned subsequently for follow-up examination.

CASE II. R. C., No. 312075, a thirty-one year old male was first admitted to the Albert Merrit Billings Hospital in June, 1943. Three months before admission he had been ill with a pharyngitis which subsided after several days. Subsequently, the left shoulder, both knees and the right ankle became painful and swollen. Approximately three weeks before admission the patient developed lower abdominal cramping, pain and diarrhea; five to six semiformed, liquid stools containing bright red blood and mucus were passed daily. Additional symptoms included anorexia, a loss of 40 pounds in weight and marked weakness. Physical examination disclosed a markedly undernourished male. The skin was clear but very dry. The heart and lungs were normal. There was marked tenderness over the course of the colon. All joints appeared normal grossly; there was no visible edema of the extremities. The erythrocyte count measured 3.88 million and the hemoglobin 12.5 Gm. The leukocyte count was 19,350; 82 per cent of the cells were of the polymorphonuclear series. The value for total plasma proteins was 4.85 Gm. per cent; the albumin measured 3.24 Gm. and the globulin 1.61 Gm. Numerous examinations of the stools were

FIG. 3. Case 1. Biopsy from the edge of ulcer showing hyperkeratosis and benign hyperplasia of the epidermis. There is dilatation of the numerous blood vessels and the collagenic tissue is markedly edematous. × 125.

FIG. 4. Case 1. Biopsy from the base of the ulcer showing infiltrate of polymorphonuclears, plasma cells, lymphocytes and connective tissue cells. × 130.

negative for E. histolytica, other parasites and pathogenic organisms. Agglutination tests with the patient's serum against typhoid, salmonella and dysentery organisms were negative. Proctoscopy revealed a friable, edematous, bleeding mucosa, typical of the acute stage of nonspecific ulcerative colitis.

The patient was treated medically for a period of 212 days. Therapy included the use of a bland, low residue diet, sedatives, antispasmodics and large amounts of vitamins. Sulfadiazine was administered in doses of 4.0 Gm. daily for periods of seventeen, five and eleven days. Sulfathalidine was given in doses of 12.0 Gm. daily for twenty days. Subsequently, sulfadiazine was resumed in quantities of 12.0 Gm. daily for eight days and then 4.0 Gm. daily for nine days. The patient received twenty transfusions of 600 cc. of whole blood, eight infusions of 500 cc. of plasma, large quantities of 2½ per cent amigen in 10 per cent glucose solution and 10 per cent amigen in isotonic saline solution, 5 per cent glucose in saline as well as 10 per cent glucose in distilled water. No significant improvement occurred during this period of intensive therapy. The temperature remained almost constantly elevated, with sharp rises to levels of 39 and 40°C. As many as eighteen liquid stools containing blood and mucus were passed daily. A severe ulceration developed about the anal sphincter, with extensive sinus formation and the drainage of thick, mucopurulent exudate. On the 209th hospital day the patient passed per rectum approximately 150 cc. of blood together with liquid feces and purulent exudate. There was continued slight loss of weight and persistent, moderately severe secondary anemia. The total plasma protein varied at first from 4.78 to 5.17 Gm. per cent; after administration of blood, plasma and amigen the values ranged from 5.34 to 6.32 Gm. per cent.

On the eighty-ninth hospital day several nodular lesions appeared on the nape of the neck. (Fig. 5.) Similar lesions developed almost simultaneously on the forehead, chest and back. The lesions represented acute inflammatory infiltrates with pustule formation in the pointed center and an acute erythematous border. The differential diagnosis included nodular toxic eruption, atypical erythema multiforme or septicemic emboli. Blood culture was negative. Bacteriologic study of the purulent exudate showed no bacteria. Microscopic examination of a biopsy specimen of one of the lesions was inconclusive. After several weeks the eruption gradually subsided but, three months later, similar lesions again developed on the nape of the neck. The character of the eruption now was less infiltrated and partly herpetiform, with groups of vesicles on an erythematous base. Several weeks later a confluent erythematous papular eruption was noted on the posterolateral aspects of the neck, suggestive of toxic dermatitis. This gradually subsided without therapy.

An ileostomy was performed on the 213th hospital day. The patient's postoperative recovery was excellent. The temperature rapidly returned to normal. The patient gained 25 pounds in weight and he was discharged from the hospital forty-four days after operation. Improvement continued but five to six bloody

FIG. 5. Case II. Nodular and papulopustular lesions on the neck.

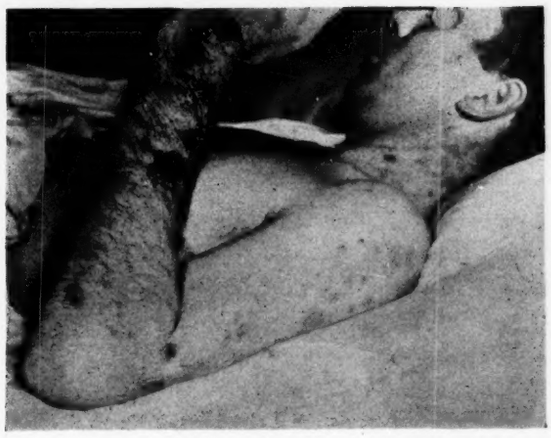

FIG. 6. Case II. Pyoderma left forearm. Note the many scars of previous lesions on the left arm and the neck.

discharges were passed from the rectum daily. The patient was readmitted to the hospital in April, 1945. Approximately one month earlier, furuncles had reappeared in various parts of the body. For one week the patient had experienced pain in both lower extremities. Physical examination revealed a fairly well nourished male who did not appear ill. There were many solitary reddened nodules, some of them displaying a purulent center, on the neck, arms, trunk, hips and left leg. (Figs. 6 and 7.) The ileostomy was functioning normally. Laboratory studies indicated moderately severe secondary anemia; the leukocyte counts varied from 11,000 to 16,450. Total plasma proteins ranged from 5.9 to 6.76 Gm. per cent. Proctoscopy disclosed a markedly inflamed friable, bleeding mucosa, covered with a bloody, mucopurulent exudate. The patient was treated with sedatives, feosol and sulfadiazine. Nine transfusions of 600 cc. of whole blood, 500 cc. of plasma, large amounts of amigen and isotonic saline solutions were administered. A total of 9,860,000 units of penicillin were given intramuscularly from the twelfth to the seventy-third hospital days. Two days after penicillin therapy was instituted the pyogenic lesions increased in number and severity. The eruption now consisted of follicular pustules and perifollicular infiltrates; a marked tendency to necrosis was noted in the larger lesions. The lesions closely resembled those present during the previous hospitalization period. A diagnosis of pyoderma gangrenosum was made at this stage. Cultures of the purulent exudate revealed hemolytic Staph. aureus and B. pyocyaneus. Therapy consisted of warm, moist applications of potassium permanganate in a concentration of 1:8000 for five to fifteen minutes twice daily and the local application of 20 per cent ammoniated mercury ointment. Many of the lesions improved after three weeks of treatment. Colectomy was performed on the fifty-eighth hospital day. The entire bowel was shrunken and injected. Large lymph nodes were present in the thickened mesocolon. Gross and microscopic examinations of the bowel revealed the usual features of chronic non-specific ulcerative colitis. Recovery was uneventful and the patient was discharged seventeen days after operation. His subsequent course was remarkably good. Two and one-half months after colectomy the patient weighed 170 pounds, a gain in weight of 80 pounds since the initial hospitalization in 1943. All skin lesions had healed completely. His health remained good until January, 1948; intestinal obstruction with gangrene of the bowel developed at this time and progressed to fatal termination despite surgical intervention.

CASE III. D. O'D., No. 152942, a thirty-seven year old female school teacher, was first hospitalized in June, 1940. Approximately five years previously she had become ill with alternating diarrhea and constipation, generalized abdominal pain, loss of weight and fatigue. In April, 1936 blood and mucus appeared in the stools. A diagnosis of chronic non-specific ulcerative colitis was made and the patient responded to therapy emphasizing bed rest. Her subsequent course was characterized by frequent recurrences related to nervous tension, exertion and work. Improvement usually resulted when the patient stopped teaching and obtained adequate rest.

FIG. 7. Case II. A higher magnification of lesions shown in Figure 6. Some of them have herpetiform features (grouped vesicles).

Physical examination revealed a slender, pale young woman. The skin appeared normal. There was a swelling in the right tonsillar fossa with necrosis and ulceration. The erythrocyte count was 2.54 million, the hemoglobin 8.0 Gm. and the leukocyte count 12,000. The Wassermann and Kahn tests were negative. The stools were negative for parasites and pathogenic bacteria. Proctoscopic examination previously had revealed the typical features of non-specific ulcerative colitis. The patient received a transfusion of 450 cc. of whole blood and after spontaneous drainage of the peritonsillar abscess she was discharged from the hospital.

She was hospitalized again in January, 1941. Bloody diarrhea had recurred one month earlier. One week before admission she experienced loss of appetite and generalized muscular aching. At the same time several red and tender papules appeared on the back along the thoracic spine. These became pustular and similar lesions soon developed over the trunk and extremities. The temperature rose to 102°F. and a presumptive diagnosis of chickenpox was made. However, the patient had had the usual exanthemas, including chickenpox, during childhood. Physical examination revealed a poorly nourished female who appeared distressed but not acutely ill. Reddened, tender variably sized papules and occasional large pustules were present over the entire body. Some of the lesions were ulcerated and the bases of the ulcers were purulent. The diagnosis of pyoderma gangrenosum was made. The erythrocyte counts ranged from 3.58 million to 3.88 million; the hemoglobin 8.8 to 11.0 Gm. and the leukocyte count at first varied from 10,200 to 20,000; the white count later returned to normal. Many stools were negative for parasites and pathogenic bacteria but contained occult blood. The plasma

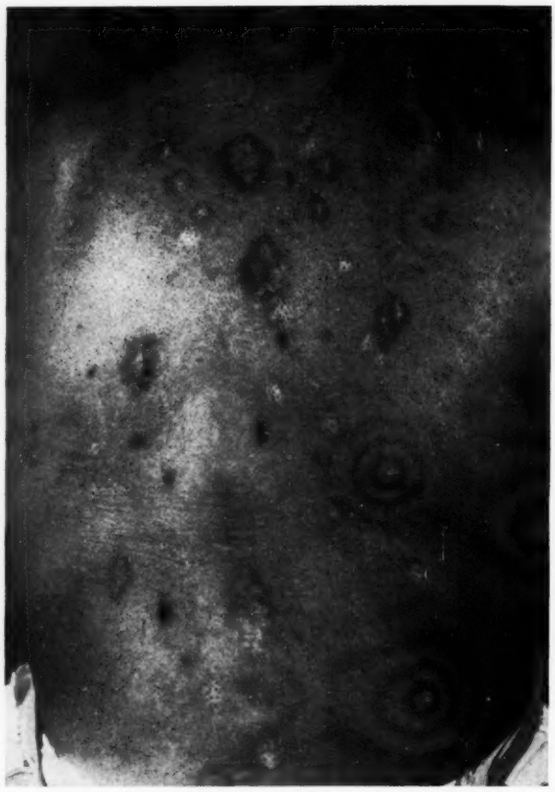

FIG. 8. Case III. Hypertrophic and atrophic, hyperpigmented and depigmented scars of the skin over the back in a patient with chronic non-specific ulcerative colitis and healed pyoderma gangrenosum.

proteins on two occasions measured 5.38 and 5.45 Gm. per cent; the albumin was 2.59 and the globulin 2.79 on one determination. Three blood cultures yielded no growth. Two cultures of the purulent material from the skin lesions were negative. X-rays of the chest revealed normal lung fields and the presence of cervical ribs.

The colitis was treated by bed rest, use of a bland diet, bismuth subnitrate and vitamins. Sulfanilamide, in amounts of 5.6 Gm. daily, was given from the twenty-ninth to the thirty-eighth hospital days. The skin lesions were treated by the daily general application of ultraviolet irradiation and local application of tincture of gentian violet. Improvement occurred slowly but gradually. The ulcerations on the neck proved more resistant to therapy and drained purulent exudate for several weeks. Marked improvement was noted on the seventieth day. Many of the ulcerations had healed with residual atrophic scarring. At the end of three months all skin lesions had healed and the patient was discharged from the hospital.

In July, 1945 the patient suffered a recurrence of the ulcerative colitis and she lost 15 pounds in

weight. At this time also there was a recurrence of the cutaneous lesions, involving especially the back and both legs. The patient was hospitalized elsewhere and gradually recovered. The skin lesions slowly healed, with production of thin, atrophic scars.

The patient was last seen in July, 1946 at which time she appeared to be under considerable emotional tension. Two or three moderately formed stools without gross blood were passed daily. There were no ulcerations of the skin but many atrophic scars of former lesions were present. Figure 8 demonstrates the end stages of pyoderma gangrenosum in this case.

COMMENT

Pyoderma gangrenosum may be a serious complication of chronic non-specific ulcerative colitis and, as illustrated by Case I, may assume greater clinical significance than the primary disease. Chronicity of the lesions and resultant disability of the patient tax the ingenuity and patience of the most resourceful physician. It is apparent from these case studies that the bacterial flora of these pustular and ulcerative lesions is not uniform and not pathognomonic and that some of the purulent lesions may even be sterile. Correspondingly, large quantities of sulfonamides and penicillin have little value either prophylactically or therapeutically. Obviously decreased resistance of the skin organ and its great tendency to tissue necrosis is a more important factor in the pathogenesis of pyoderma gangrenosum than is bacterial infection. The decrease in resistance, however, does not depend solely on the severity of the colon infection or on the subsequent state of malnutrition. Pyoderma gangrenosum developed in the first patient when the ulcerative colitis was in a quiescent state and it recurred in the second patient despite a satisfactory clinical response to ileostomy. Yet, the further course in Case II indicates that there must be a direct connection between primary bowel disease and skin manifestations for after the infected colon was resected the pyoderma subsided completely and permanently. At the present time it seems that control of the underlying chronic disease and restoration of a normal state of nutrition are the best methods for prevention and successful treatment of pyoderma gangrenosum.

SUMMARY

Three cases of pyoderma gangrenosum complicating chronic non-specific ulcerative colitis are described in detail. No pathognomonic flora was found and some of the purulent lesions were sterile. Large quantities of sulfonamides and penicillin were of no value either prophylactically or therapeutically. Improvement in Case I followed improvement of the general condition of the patient and persistent local therapy with ultraviolet light and silver nitrate solutions. Complete recovery in Case II was achieved after resection of the infected colon and restoration of a normal state of nutrition. The third patient recovered after use of ultraviolet light therapy, local application of tincture of gentian violet and control of the chronic non-specific ulcerative colitis.

REFERENCES

1. Bargen, Arnold J. Complications and sequelae of chronic ulcerative colitis. *Ann. Int. Med.*, 3: 335–352, 1929.
2. Ricketts, William E. and Palmer, Walter L. Complications of chronic ulcerative colitis. *Gastroenterology*, 7: 55–66, 1946.
3. Brunsting, A., Goeckerman, William H. and O'Leary, Paul A. Pyoderma (echthyma) gangrenosum; clinical and experimental observations in 5 cases occurring in adults. *Arch. Dermat. & Syph.*, 22: 655–680, 1930.
4. Lane, Clinton W. and Stroud, C. Malone. Pyoderma gangrenosum. *Arch. Dermat. & Syph.*, 27: 460–471, 1933.
5. Cohen, Melton H. Pyoderma gangrenosum. A deficiency disease complex. *Arch. Dermat. & Syph.*, 33: 813–824, 1936.
6. Cowet, Max P. Pyoderma complicating ulcerative colitis. *Am. J. Surg.*, 38: 364–368, 1937.
7. Jankelson, I. R. and Massell, B. F. Pyogenic skin lesions accompanying chronic ulcerative colitis. Report of 5 cases. *Am. J. Digest. Dis.*, 3: 19–22, 1936.
8. Jankelson, I. R. and McClure, Charles W. Skin lesions during the course of chronic ulcerative colitis. *Acta dermat.-venereol.*, 41: 255–267, 1940.
9. Mintzer, Ida J. Pyoderma gangrenosum, onychogryphosis and with ulcerative colitis. *Arch. Dermat. & Syph.*, 40: 541–543, 1939.
10. Felsen, Joseph. Multiple necrotizing skin lesions in chronic ulcerative colitis. *New York State J. Med.*, 41: 2228–2231, 1941.
11. Felsen, Joseph. Bacillary Dysentery, Colitis, Enteritis. Philadelphia, 1945. W. B. Saunders Co.

Unusual Strain of Pseudomonas Aeruginosa Recovered from the Urinary Bladder

Effects of Streptomycin

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PSEUDOMONAS aeruginosa (B. pyocyaneus) which was first isolated by Gessard[5] in 1872, has been recognized for years as the organism which produces "blue pus" and much speculation has arisen concerning its rôle as a primary invader and the degree of pathogenicity it shows in human beings. Since 1890, there have been divergent views concerning the rôle this organism plays in disease. Marthen[9] (1890), in an essay discussed the implications of the "blue pus organism" and emphasized the occurrence of paralysis in patients and laboratory animals infected with virulent strains of B. pyocyaneus. He noted that the bacteria-free filtrate contained: (1) The greenish pigment "pyocyanine" and (2) an exotoxin which produced various effects including albuminuria and paralysis of varying degree when injected into laboratory animals. He also stated that immunization could be attained by inoculating animals with sub-lethal doses of bacteria.

In proof of the virulence that may be displayed by B. pyocyaneus in infections, Edel[3] collected several case histories in which fatalities were described. Bernhardt[1] and Klieneberger[6] reported cystitis and nephritis which were directly attributable to the organism. Loder[8] found that experimental animals frequently succumbed within six to twelve hours after inoculation, showing a severe terminal drop of body temperature. General infections with Ps. aeruginosa, while of rare occurrence in healthy adults, are more common in children and debilitated adults. (Musser and Sodeman.)[10] These investigators maintained that paralysis of smooth muscle and paresis of the leg musculature with subsequent atrophic changes may follow absorption of the pyocyaneus toxin. Clawson and Young[2] isolated hydrocyanic acid from the exotoxin produced in broth cultures of Ps. aeruginosa but to a less extent from *in vivo* examinations.

Although considerable literature has accumulated on the bacteriological and to a less extent on the clinical aspects of the Ps. aeruginosa, little work has been done in differentiating various strains of bacilli constituting this group. Although bacteriologists have often discussed the question of bacterial variability or mutation, they have rarely referred to examples of urinary tract infections with atypical organisms. This is not solely an academic problem, because it is possible that in a changed form a bacterium may play an entirely different rôle than the parent strain.

It is known for example that the relative degree of virulence of certain bacteria can be roughly estimated by the character of the colonies they produce on agar plates. Those in the so-called "S" or smooth category are believed to exhibit increased virulence. The second group, known as the "R" or rough group, (because of the irregular contours which the colonies show on agar

plates) contains organisms which show less virulence. The third category, of which only slight mention has been made in medical literature, is known as the "M" or mucoid group because of the characteristic mucoid appearance of the colonies. Bacteria in this category frequently have distinct capsules and show higher grades of virulence. Organisms belonging to the three groups may be present singly or in association. In this paper we propose to deal with the mucoid variant of Ps. aeruginosa.

CASE REPORTS

CASE 1. Mr. J. P. was operated on by the senior author March 13, 1946. A right nephrectomy and subtotal ureterectomy was performed for suppurative pyelonephritis, ureteritis and multiple renal calculi. During the course of a routine follow-up urological examination on April 9, 1946, gram-negative encapsulated rods were recovered from the bladder urine. Urine from the left kidney was negative on smear and sterile on culture. Colonies on blood agar plates were distinctive because of mucoid, massed appearance and a striking hemolytic tendency.

The organism, a blunt rod occurring singly, in pairs and in short chains, presented well defined capsules on an ordinary Gram stain. On Leifson's modification of the flagella stain, three flagella were noted, two at one pole and one at the other. After secondary cultivation, however, the capsules could be seen only when treated with regular capsule stains. The organism fermented dextrose but merely produced an insignificant amount of acid. In view of the close similarity to Friedländer bacillus and Aerobacter aerogenes, it was deemed advisable to carry out further studies before the specific identity of the organism could be established. Following inoculation of routine differential media the organism was found to be a mucoid variant of Ps. aeruginosa. Owing to close resemblance to Pseudomonas fluorescens, differentiation could be made only by establishing its pathogenicity by means of animal inoculations. *In vivo* studies readily disclosed that we were dealing with a virulent bacterium of great

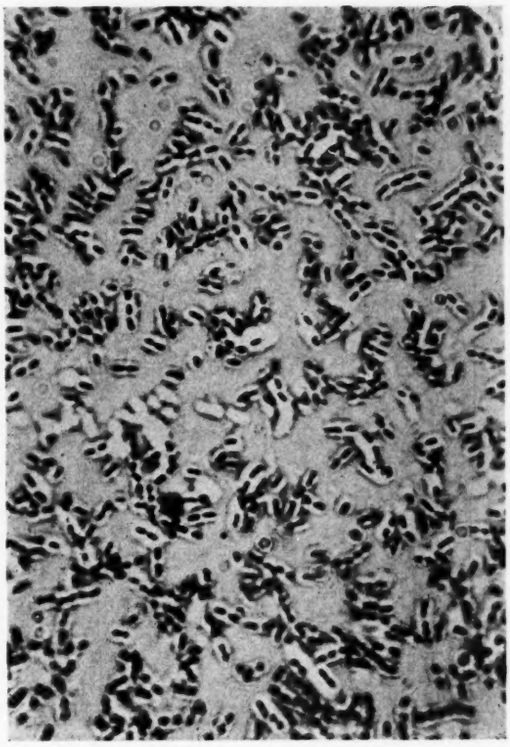

FIG. 1. Mucoid variant of B. pyocyaneus on primary isolation showing capsule. × 1250.

toxicity which in doses as low as $\frac{1}{10}$ ml. proved rapidly fatal to mice weighing 20 Gm. Before death all inoculated mice showed evidence of hind limb paralysis.

Smears of the centrifuged urine showed many Gram-negative rods measuring approximately 0.5 to 0.6 by 1.5 microns. Blood agar plates were streaked and broth tubes inoculated with the sediment. After twenty-four hours luxuriant growth was noted on the plates and in the tubes. The colonies were grayish, presented smooth borders and were beginning to assume a massed appearance. When touched with the inoculating needle, they were found to be extremely mucoid as shown by their tendency to follow the needle in long strings. Microscopically the organism appeared as a gram-negative rod with a well defined capsule. (Fig. 1.) It was motile and produced no acid or gas on Kligler's iron agar, thus differentiating it from the Klebsiella pneumoniae and Aerobacter aerogenes. Broth cultures contained a green pigment which was soluble in water and chloroform. Nitrates were reduced and litmus milk rapidly peptonized with production of alkali. Gelatin and Loeffler's

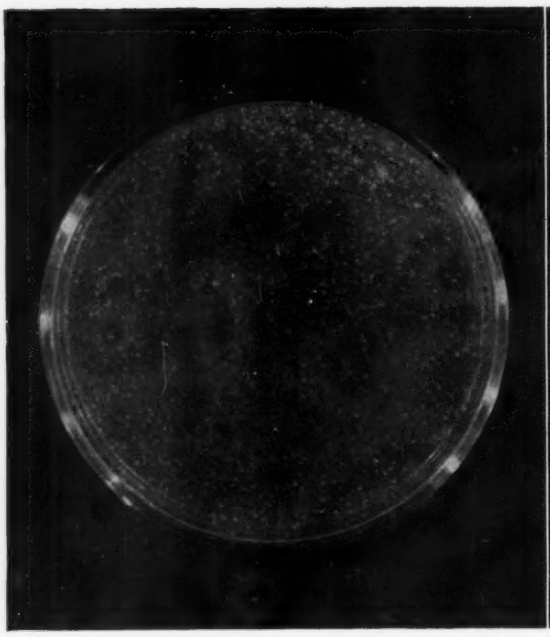

FIG. 2. Colonies of K. pneumoniae on tryptose phosphate agar.

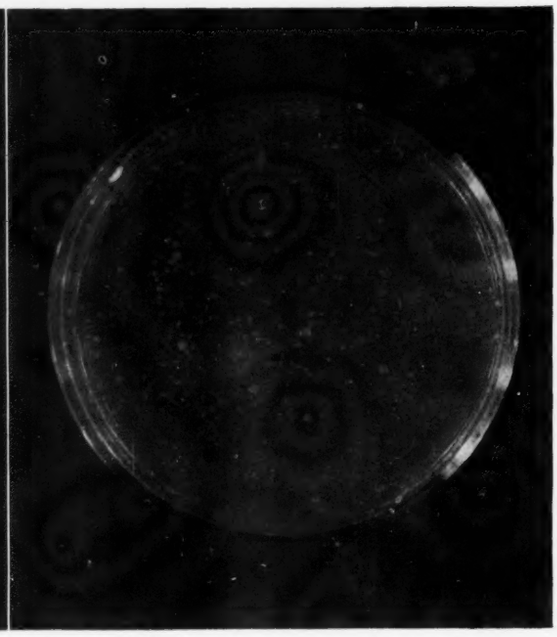

FIG. 3. Colonies of B. pyocyaneus on tryptose phosphate agar.

serum were promptly liquefied and the blood hemolyzed.

DIFFERENTIATION FROM KLEBSIELLA PNEUMONIAE (FRIEDLÄNDER BACILLUS)

Klebsiella pneumoniae, which occasionally is isolated from the urine, closely simulates the mucoid variant of Ps. aeruginosa, especially in regard to the appearance of its colonies on blood agar plates. (Figs. 2 to 5.)

This organism (first described by Friedländer[7] in 1882), is a gram-negative rod measuring approximately 0.3 to 0.5 by 5.0 microns. It is found alone and in pairs; it is encapsulated but shows no motility. It ferments dextrose, sucrose, lactose, levulose and galactose with the formation of acid and gas. It may ferment maltose but not mannitol. Sugar fermentations are unreliable, however, and serological typing should be done for correct identification. Nitrates are reduced to nitrites, litmus milk is acidified but gelatin is not liquefied. Colonies on blood agar plates are large, grayish in color and present smooth or rough borders and a massed appearance. The blood is not hemolyzed.

DIFFERENTIATION FROM AEROBACTER AEROGENES

Aerobacter aerogenes (discovered by Kruse[7] in 1896), is a gram-negative rod measuring approximately 0.5 to 0.8 by 1.0 to 2.0 microns and appears singly. It may be motile or non-motile and is frequently encapsulated. Dextrose, lactose, maltose, levulose and galactose are fermented with the production of acid and gas. Sucrose may be fermented and nitrates are reduced to nitrites. The blood is not hemolyzed, gelatin is not liquefied but litmus milk is acidified. On blood agar plates the colonies are large, appear grayish, are of a mucoid, heaped appearance and may present smooth or rough borders.

LABORATORY PROCEDURE

Errors in diagnosis are inevitable in view of the occasional tendency to identify organisms by the appearance of their colonies on blood agar plates. To avoid these errors when dealing with colonies

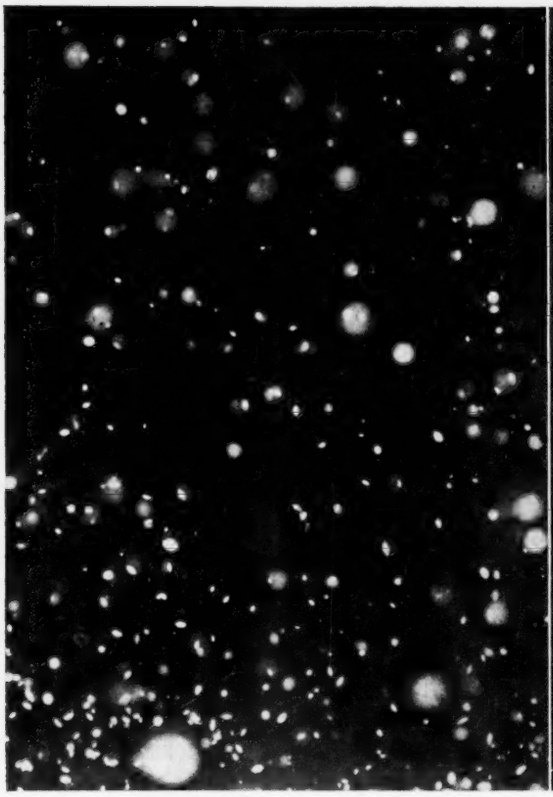

FIG. 4. Colonies of K. pneumoniae. × 500.

FIG. 5. Colonies of smooth mucoid variant of B. pyocyaneus. × 500.

similar to those previously described we have established the following routine. A single colony is examined for purity by the Gram stain. A pure culture of the gram-negative rod is then planted on Kligler's iron agar. Care must be taken, not only to stab the butt of the slant, but also to streak the surface of the agar. After twenty-four hours the agar is examined and a tube of broth media is inoculated in order to demonstrate motility. If the slant appears unchanged and a strong odor is present and if the broth tube discloses a motile rod, it may be presumed that the organism is one belonging to the group of Ps. aeruginosa. If the agar tube is of a uniform yellow (with bubbles) and if acid and gas are present, inoculations are promptly made into dextrose, lactose, sucrose, maltose, mannitol, nitrate media and litmus milk. Clark and Lubb's media is used for the determination of methyl red and Voges-Proskauer's correlation is used if the organism ferments maltose in order to differentiate it from E. coli. If maltose does not ferment and the remainder of the tests prove positive, it may be presumed that the organism is K. pneumoniae. If maltose is fermented, all the other tests (including Voges-Proskauer) prove positive, the methyl red test negative and the organisms are *not* agglutinated by pneumoniae antiserum the organism may be identified as A. aerogenes. If the methyl red test is positive and a Voges-Proskauer test negative, the organism is E. coli.

IN VIVO EXPERIMENTS WITH STREPTOMYCIN

Two rabbits were inoculated intravenously with 3 cc. of suspension of organisms washed with sterile saline. Rabbit No. 1 received 10,000 micrograms of streptomycin three hours after inoculation and a similar dose four hours later. The temperature rose from 102.2°F. to 104°F. six hours later. Within forty-eight hours after

inoculation, the animal began to show signs of paralysis of the hind limbs, the body temperature dropped to subnormal and bowel movements became loose and frequent. Death ensued a few hours later.

Postmortem examination was immediately performed and revealed: (1) Bilateral hemothorax with approximately 15 cc. of sanguineous, frothy fluid in each pleural sac as well as multiple abscesses in both lungs. A pure growth of B. pyocyaneus was recovered on smear and culture; (2) the heart muscle showed a few miliary abscesses and B. pyocyaneus was found in the heart's blood; (3) miliary abscesses were also seen in the liver and kidneys. The central nervous system was not examined.

Rabbit No. 2 was eight months old and weighed 3 pounds; it was inoculated intravenously with 3 cc. of a broth culture. Before inoculation the rabbit's temperature was 101.8°F. Twenty-four hours later the rabbit received 20,000 micrograms of streptomycin intravenously; the temperature then dropped to 100°F.; the animal appeared acutely ill and refused food. In five days, however, it had completely recovered except for a necrotic area at the site of the original inoculation. There were no sequelae. The rabbit was again inoculated with 4.5 cc. of a broth culture, and the only reaction noted was an erythema at the site of inoculation. Although under careful surveillance for three weeks no ill effects were noted.

Using the same encapsulated organism which had been transplanted weekly on Bacto tryptose broth media for two months, 5 cc. of a month old growth was injected intraperitoneally into a female albino guinea pig. The animal succumbed in thirty-six hours. At postmortem examination multiple small abscesses were discovered in the left lung, kidneys and adrenals. The stomach, liver and intestine were covered with a malodorous, bluish-white mucopurulent exudate. The liver and spleen showed chronic passive congestion and inflammatory changes. The urinary bladder was also covered with a fibropurulent exudate. The spinal cord was apparently uninvolved but the subarachnoid space over the brain was filled with mucopurulent exudate. The brain, however, disclosed no pathological changes. Smears taken from the affected organs showed many macrophages and gram-negative encapsulated rods (Ps. aeruginosa).

In order to ascertain the toxic source the following experiments were carried out:

(1) A ninety-six-hour tryptose broth culture of B. pyocyaneus (mucoid variety) was filtered through a Seitz filter. The pigment was extracted by repeated washings with chloroform. The pure pigment was then evaporated to dryness. This crystalline substance was dissolved in 5 cc. of distilled water and sterilized in the autoclave under 15 pounds of pressure for fifteen minutes. The solution was then inoculated intraperitoneally into a female albino pig. Careful observation of the animal for seven days disclosed that it suffered no ill effects, thereby proving that the pigment pyocyanine was innocuous. (2) Following the intraperitoneal injection of 8 cc. of toxin filtrate into a guinea pig the animal had a convulsive seizure which lasted for twenty-five minutes. After one hour it was semicomatose and showed signs of paralysis of the hind limbs. Complete recovery occurred in seventy-two hours. (3) An albino pig received 5 cc. of a four-week old tryptose broth culture of B. pyocyaneus which was a daughter strain of the original mucoid colony isolated two months previously. Five minutes after the injection the animal developed urinary incontinence, incomplete hind limb paralysis and loss of equilibrium. It lost all interest in food. Ten minutes after the inoculation it was semicomatose and developed complete paralysis of the hind limbs making it impossible for it to remain upright. Respirations were very rapid. Death ensued forty-eight hours after inoculation.

These experiments indicated that (1) even old cultures of the mucoid variant of Ps. aeruginosa retain their high virulence; (2) the bacteria-free filtrates are not fatal to laboratory animals and (3) the pigment pyocyanine apparently plays no rôle in the pathogenicity of the organism. It appears, therefore, that the toxicity of this bacillus is probably due to an endotoxin which is capable of causing a multiplicity of visceral lesions.

On June 18, 1946, a third culture was made of the bladder urine of the patient which again disclosed the same organism. A 4 pound albino

female rabbit was inoculated with 4 cc. of a twenty-four-hour culture (washed suspension). The only result was to make the animal extremely lethargic. Two days later the animal received 25 cc. of a seventy-two-hour tryptose broth culture (organisms and toxin) intravenously. Within three minutes it became restless and after five minutes had two convulsive seizures and expired after the second convulsion.

Postmortem examination disclosed perihepatitis, multiple liver abscesses and hemorrhage in the left orbit. There was also a pronounced leptomeningitis hemorrhagica involving the meninges of the brain and cord with hemorrhages and purulent exudate within the substance of these structures. Smears from the liver showed thick encapsulated rods (Ps. aeruginosa) identical with those of the original culture.

Treatment of the patient with streptomycin was now begun. The initial dose (May 7, 1946), was 500,000 micrograms which was followed by a similar dose three hours later; then 100,000 micrograms were administered at three-hour intervals. A urine culture made after the second dose was sterile and remained so until June 7, 1946, when a pure culture of a "smooth" strain of Ps. aeruginosa was isolated. Careful study of this organism showed it to be non-encapsulated, amotile and much less virulent than the mucoid strain as was shown when it was injected intraperitoneally into a 4-pound male rabbit. The only result was the formation of an abscess at the site of inoculation. A urine culture (June 19, 1946), however, again revealed a pure culture of the mucoid strain, the organism disclosing characteristics which were identical with those of the original strain except that its virulence was notably diminished.

At this point we concluded that (1) streptomycin in a dosage of 5,000,000 micrograms had only a transient inhibitory effect on the organism; (2) one month after discontinuance of the antibiotic we recovered another strain (smooth) of Ps. aeruginosa; (3) twelve days later a culture of the bladder urine again showed the original strain (mucoid) but of a reduced virulence.

The question naturally arose as to whether or not we were dealing with an example of mutation of bacteria or with two different strains of the same group. In the former instance it would be necessary to postulate that streptomycin was instrumental in causing (1) noteworthy but temporary bacteriostasis so that for one month after discontinuance of the drug repeated cultures were sterile; (2) a change in physical characteristics of the bacillus, in that the colonies lost their mucoid appearance and the organism its characteristic capsule; (3) a definite decrease in virulence and pathogenicity. In the last noted instance we must assume the simultaneous presence of both strains of organisms at the time of preparing the original culture, in which the predominant strain (namely, the mucoid variety) completely overgrew and masked the other (smooth) strain. Upon the administration of streptomycin there occurred an abrupt inhibition of both strains, more sustained, however, in the case of the mucoid variety with the result that on cultures taken one month after discontinuance of the antibiotic only the smooth species was recovered. A later culture, however, showed the mucoid organism again active and predominant but displaying decreased virulence.

On July 7, 1946, Mr. J. P. reported feeling well but complained of occasional increased urinary frequency. Urinalysis showed albumin 2+ and many leukocytes. Culture of the bladder urine again showed the smooth mucoid encapsulated variant of Ps. aeruginosa.

Two rabbits were inoculated, one intraperitoneally with 11 cc. of a ninety-six-hour washed suspension of Ps. aeruginosa containing toxin and pyocyanine and the other intravenously with 3 cc. of the same suspension. The first rabbit succumbed in twelve hours and the second five minutes after the inoculation.

Necropsy performed on rabbit No. 1 disclosed pneumonitis involving the left lung and miliary abscesses of the right lung. There was hemorrhagic infiltration of the wall of the large bowel, most pronounced in the cecum. The stomach showed a spontaneous laceration of its wall near the cardia, measuring approximately 3 cm., with a large amount of gastric contents present in the upper abdomen. There were several abscesses in the right lobe of the liver. The kidneys and adrenals were apparently unaffected. The spinal cord showed many hemorrhages. Gram-negative encapsulated rods

were found in smears taken from abscesses in the liver and lung.

In view of the highly pathogenic character of this organism in animal experiments and the few symptoms shown by the patient, we instilled 2.5 cc. of a ninety-six-hour broth culture into the bladder of a full-grown female rabbit through a ureteral catheter. After seventy-two hours the rabbit developed urinary frequency but no other symptoms. Specimens of urine showed many leukocytes and encapsulated rods (Ps. aeruginosa) in smears. Nine days later despite positive urinary data the animal was completely asymptomatic.

Case II. Mr. C. H. Y., forty-three years of age, was first seen on December 18, 1933, complaining of painful hematuria and increased diurnal and nocturnal urinary frequency of four days' duration. During the previous five years he had sustained attacks of right renal colic and for four and one-half years attacks of left renal colic. A complete urological examination disclosed a small calculus in the bladder, moderate hydronephrosis of the left pelvis, hypertension (174/80) and mitral stenosis. The vesical calculus was removed cystoscopically.

The patient was next seen in consultation on August 15, 1946. During the previous several weeks he had been under medical care for hypertension, his blood pressure varying between 230/140 and 170/80. A flat film of the kidneys disclosed a large stag-horn calculus in the pelvis of the left kidney. During the previous week his temperature ranged between 101°F. and 102°F. A complete urological examination elsewhere showed a well functioning kidney and normal pelvis on the right side. The left pelvis was moderately dilated especially the upper calyx. Treatment consisted of ureteral drainage of the left pelvis. During the consultation period the temperature was 103°F. and definite left costovertebral tenderness was elicited. Primary cultures from the left kidney were reported showing Staphylococcus albus. Subsequently, a pure growth of E. coli and finally Ps. aeruginosa (mucoid variant) were observed. Presurgical diagnosis: Left renal calculus and suppurative pyelonephritis (multiple abscesses).

Operation was performed August 16, 1946, by the senior author. Under spinal anesthesia the left kidney was exposed through a 7 inch Albarran incision. The organ was moderately enlarged and presented considerable perinephritis. Upon stripping the capsule groups of miliary abscesses were found on the anterior surface of the kidney above the hilus and over both renal poles. There was a large, hard, stag-horn calculus in the renal pelvis. The calices were moderately dilated especially the superior one. In view of the presence of sufficient renal parenchyma it was deemed advisable to conserve the kidney. The calculus was removed through a nephrostomy opening and the pelvis drained with a soft rubber tube. The operation was concluded by draining the renal fossa and closing the wound in layers. A transfusion of 500 cc. of blood was given immediately following the operation.

During the postsurgical period the general condition of the patient was excellent despite failure of the temperature to subside. (101°F. to 102°F.) Drainage through the nephrostomy tube was scanty for the first forty-eight hours but finally increased to 100 to 200 cc. daily. Streptomycin was administered in doses which will be described at a later point. Approximately seven days after surgery the patient developed a persistent severe hematuria. Several transfusions were given and vitamin K administered but bleeding continued. In view of our inability to control the bleeding plus the continued fever, the persistence of positive cultures of Ps. aeruginosa (mucoid variant) and despite the administration of 13,000,000 micrograms of streptomycin, it was deemed advisable to remove the kidney.

The operation was performed on August 30, 1946. Under cyclopropane anesthesia the kidney was exposed by reopening the original wound. Profuse bleeding occurred as soon as the nephrostomy tube was removed. The kidney was enlarged, boggy and felt very warm to the touch. A moderate number of cortical abscesses could still be seen in the renal cortex but these were not as conspicuous as they were at the time of the previous operation. The renal pedicle and ureter were doubly ligated and the kidney quickly removed. The renal fossa was drained and the wound closed in layers. A transfusion

of 500 cc. of blood was administered at the conclusion of the operation.

The pathologist's report (Dr. A. Schifrin) was as follows: Macroscopic: "The specimen consists of a large kidney which has been stripped of its capsule. It measures 10 × 7 × 6.5 cubic centimeters. No stones are present within the specimen received (the calculus, it will be remembered, was removed at previous operation). The pelvis had been opened and was moderately dilated. Several large friable and firmly adherent blood clots are present. At one pole adjacent to a dilated calyx there is a triangular, firm, partly whitened blood clot. The pelvic wall at this site is hemorrhagic and ulcerated. Other parts of the pelvis and some of the calices show hemorrhagic indurations and ulcerations of their wall. The renal parenchyma is broad and its markings are indistinct. They contain numerous white and hemorrhagic streaks. The renal surface (stripped of its capsule) shows numerous small and larger elevations and depressions, most of which correspond to the streaked whitish and hemorrhagic parenchyma noted above. The uretero-pelvic junction is not dilated.

"Microscopic: Kidney. Section through the pelvis and calices shows extensive ulceration of the mucosa with an overlying broad zone of clotted blood. The base of the ulceration is lined by granulation tissue containing numerous small blood vessels and showing interstitial hemorrhage and infiltration by numerous round cells, scattered polys and numerous plasma cells. Fibrosis is present. There are numerous foci of interstitial infiltration of the renal parenchyma by dense aggregation of round cells, plasma cells and polys. In some places these show small abscess formation with central hemorrhagic zones filled with polymorphonuclear leukocytes and necrobiotic nuclei. In places these foci are conglomerate. There is scattered interstitial fibrosis of the parenchyma with occasional foci containing dilated tubules with calcium encrusted epithelial cells. There are foci of fibrosis and renal atrophy beneath depressed areas of renal surface. The boss-like elevation of renal surface contains numerous microscopic abscesses within the subjacent parenchyma.

"Diagnosis: (1) Severe chronic and acute hemorrhagic ulcerative pyelitis and calicitis; (2) severe interstitial chronic and recurrent pyelonephritis with small abscess formations."

Following the nephrectomy the patient's temperature promptly subsided and he was discharged from the hospital after an uneventful convalescence, in excellent condition on September 11, 1946.

URINARY CULTURE STUDIES IN RELATION TO STREPTOMYCIN

A rabbit inoculated intravenously with 5 cc. of a washed suspension of the primary culture (August 17, 1946), expired in seven hours and was promptly autopsied. The examination showed extensive blood clots in the nose, mouth, rectum and urethra. Blood was present in the peritoneal, pleural and pericardial cavities. A small rupture was noted in the bladder in the region of the right ureter. Multiple abscesses were present in the kidneys, adrenals, gastric wall, pancreas, lungs, omentum and liver. Evidence of a previous massive hemorrhage was found in the brain. Ps. aeruginosa (encapsulated) was recovered on smear and culture from the various affected organs.

Streptomycin therapy was instituted on August 19, 1946. Ten doses of 500,000 micrograms each were administered at three-hour intervals, followed by forty-eight doses of 125,000 micrograms each and 5 doses of 400,000 micrograms each, using the same three-hour interval between doses. The total was 13,000,000 micrograms.

Cultures, which were taken every twelve hours, remained positive until September 8, 1946, when the first negative culture was obtained. In order to ascertain the virulence of the organism, several rabbits were inoculated intravenously with 5 cc. of washed-cell suspensions taken from the various cultures. The first four cultures showed intense virulence, the rabbits succumbing in seven to twelve hours. After 2,000,000 micrograms were administered, the colonies

changed to the rough variety and retained this characteristic throughout the remainder of the treatment until two negative cultures were obtained. However, a culture taken on September 11, 1946, again showed rough colonies (non-encapsulated).

Eight rabbits were inoculated with an organism taken from the rough colonies and of these two expired and one was sacrificed. Two rabbits showed paralysis of all their limbs which lasted for approximately five days and was followed by full recovery. Postmortem examination of the two rabbits and of the sacrificed animal showed minimal changes except for diffuse hyperemia of the viscera. A few rabbits presented abscesses at the site of inoculation.

CASE III. Mr. L. H. W., seventy-three years of age, was first seen on May 24, 1945, complaining of painless hematuria of five months' duration. A urological examination disclosed two large solid tumors situated on the posterior wall of the bladder near the vault. The prostate was enlarged.

An extensive segmental resection of the bladder was carried out on May 30, 1945, by the senior author and was followed-up with a full course of deep roentgen therapy. A transurethral resection was performed June 20, 1946. On September 1, 1946, the patient developed fulminating urosepsis with a positive blood culture of gram-negative rod (Ps. aeruginosa) appearing on September 12, 1946.

Sub-surface colonies showed extensive greening while the surface colonies appeared smooth and glistening. Transplants were made on gelatin, Loeffler's blood serum, Russell's double sugar agar medium and on the sugars maltose, sucrose, dextrose and lactose. Only fermentation of dextrose occurred but no gas was formed. The blood serum showed a mutation of the organism to the mucoid phase with extensive greening of the media and extremely slow liquefaction. The odor of trimethylamine usually associated with pyocyaneus was absent. Proteolysis was not as pronounced as in any of the previous organisms studied. Proteins were split only to ammonia and the nitrates reduced solely to nitrites. There was no tendency to hemolyze blood. Pyocyanine was present in small amounts, the prominent dye product being fluoroscein. This was shown by the fact that the dye was soluble in water with which it could be extracted from cultures.

A five-month old, white, male rabbit was inoculated intravenously at 11:00 A.M., September 17, 1946, with 5 cc. of a twenty-four-hour broth culture of the mucoid strain of the organism. The animal exhibited neurological symptoms within three hours, such as pronounced head tremor and hind limb paralysis. One hour before death the body temperature dropped from 101.6°F. (normal) to 98°F. Death occurred six hours and forty-five minutes after inoculation and was preceded by vomiting, diarrhea and severe convulsive seizures.

On opening the abdomen an odor of trimethylamine was distinctly noticeable and the undersurface of the abdominal integument presented a greenish fluorescent hue. The spleen was enlarged and congested while the liver showed several small punctate abscesses. The lungs appeared congested and a small abscess was present in the left lower lobe. The meninges over the brain showed multiple hemorrhages and a moderate amount of mucopurulent exudate. Three large abscesses were present on the undersurface of the brain. The spinal cord appeared hyperemic. Smears of all lesions showed gram-negative bacilli (non-encapsulated).

Treatment of the patient was started September 13, 1946, with 500,000 micrograms of streptomycin hydrochloride.* This dose was repeated at three-hour intervals for a total of 20,000,000 micrograms. The first negative culture was obtained at 4:00 P.M., September 15, 1946, after the administration of 7,500,000 micrograms. A second negative culture was obtained at 2:00 P.M. September 16, 1946. Although prior to the use of the antibiotic the patient was virtually moribund, within forty-eight hours after the administration of the first dose of streptomycin he was fully alert and his temperature dropped from 104°F. to normal. At the completion of streptomycin therapy all traces of sepsis had disappeared.

* A Merck product.

SUMMARY AND CONCLUSIONS

During a routine urological follow-up examination of a patient previously nephrectomized for calculous pyelonephritis, an unusual organism was recovered from the bladder urine, which was a mucoid variant of Ps. aeruginosa. The organism formed characteristic colonies on blood agar plates and disclosed microscopically well defined capsules. There was a very close similarity of the organism to Friedländer bacillus and Aerobacter aerogenes. When injected intravenously and intraperitoneally into laboratory animals, it proved to be highly virulent. However, when a suspension of the bacilli was instilled into the bladder of a rabbit it produced only a mild cystitis. Streptomycin in doses totalling 5,000,000 micrograms, although causing a noteworthy bacteriostatic effect, failed to destroy the organism. Shortly after the administration of the antibiotic, the bacterium temporarily lost its capsule and the colonies showed a distinct change in their mucoid appearance. A concomitant drop in virulence also occurred. Subsequent cultures, however, disclosed the reappearance of encapsulated rods, a return of the mucoid appearance of the colonies on agar plates and a striking increase in virulence.

An identical organism was recovered from the urine of a patient suffering from calculus and suppurative pyelonephritis involving the left kidney. Following a nephrolithotomy, decapsulation and drainage of the kidney 13,000,000 micrograms of streptomycin was administered. After 2,000,000 micrograms were given the rods lost their capsules and virulence diminished. At the conclusion of the full course of treatment, two negative cultures were obtained; a third culture, however, again showed Ps. aeruginosa (non-encapsulated). Owing to persistent, severe hematuria, failure of the fever to subside and despite the administration of 13,000,000 micrograms of streptomycin it became necessary to remove the kidney. Examination of the extirpated kidney still showed the presence of multiple abscesses. Following nephrectomy all symptoms disappeared even though organisms were still recoverable on culture from the bladder urine.

Ps. aeruginosa was also recovered from a patient with urosepsis following segmental resection of the bladder for extensive carcinoma. Blood serum from this patient showed mutation of the organism to the mucoid phase. Following the administration of 20,000,000 micrograms of streptomycin in doses of 500,000 micrograms every three hours, a complete recovery occurred despite the fact that the patient was moribund at the time treatment was instituted. In this instance the first negative blood culture was obtained after he had received 7,500,000 micrograms of streptomycin.

We believe that despite the paucity of symptoms among some patients harboring Ps. aeruginosa in the urinary tract, the organism, especially the mucoid variant, possesses a noteworthy virulence and pathogenic propensity. Although resistant to all urinary antiseptics, including streptomycin in doses recommended by the Division of Medical Science, National Research Council, it is possible that massive doses may prove bactericidal. Careful bacteriological examinations are not only necessary to establish the true identity of the various strains of bacilli belonging to this category but in the determination of effective therapy as well.

REFERENCES

1. Bernhardt, R. Der Bacillus des grünen Eiters in den Harnwegen. *Arch. f. Dermat. u. Syph.*, 52: 349, 1900.
2. Clawson, B. J. and Young, C. C. Preliminary report on the production of hydrocyanic acid by bacteria. *J. Biol. Chem.*, 15: 419, 1913.
3. Edel, M. Über die Menschenpathogenität des Bacillus Pyocyaneus. *Medizinischen Doktorwürde, Friedrich-Wilhelms Universität zu Berlin*, 1914.

4. Friedländer, C. Über die Schizomyoceten bei der acuten fibrosen Pneumonie. *Virchow's Arch. f. path. Anat.*, 87: 319, 1882.
5. Gessard, M. C. Sur les colorations bleue et verte des linge à pansements. *Compt. rend. Acad. d. sc.*, 94: 536, 1882.
6. Klieneberger, C. Pyocyaneusinfektion der Harnwegen mit hoher Aggluteninbildung für Pyocyaneusbacillen und Mitagglutination von Typhusbakterien. *München. med. Wchnschr.*, 54: 1,330, 1907.
7. Kruse, W. Bacillus aerogenes. In Flügge's Die Mikroorganismen. 2: 340, 1896.
8. Loder, A. Bacillus pyocyaneus. *Handb. d. path. Microorganismen*, 6: 149, 1929.
9. Marthen, G. Über blauen Eiter und den Bacillus Pyocyaneus. *Medizinischer Doktorwürde, Friedrich-Wilhelms Universität zu Berlin*, 1890.
10. Musser, J. and Sodeman, W. A. Pyocyaneus Infection. The Practitioner's Library of Medicine and Surgery, 13: 149, 1938.

875 *Park Ave.*

What Value Enteric Coating*

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MANY drugs tend to upset the stomach. They will, in some instances, cause nausea, heartburn, bloating, pain in the epigastrium, cramps and even vomiting. In order to avoid such local effects of the drug on the gastric mucosa they are often administered in the form of enteric-coated tablets. Enteric coatings of one kind or another have been in use since 1884 when Unna used keratin for this purpose.

The composition of the coatings differs. One widely used formula consists of a "powdered mixture of fatty acid, wax and hygroscopic vegetable components, with white shellac as a binding agent."[1] Pharmaceutical houses vary their formulas.

We do not propose to discuss at this time the advisability of enteric-coated drugs. The question for the present is whether or not the enteric coating always accomplishes the desired effect.

Noting a striking lack of uniformity in the therapeutic effects of two well known brands of enteric-coated ammonium chloride tablets, we proceeded to investigate the possible reasons therefor. We were rather surprised to learn that one of the preparations distributed by a reputable drug company failed to have any effect in four of five cases as judged by its use in congestive cardiac failure in conjunction with mercurial diuretics. The reason for its inefficacy became obvious when we found that in four cases out of five the tablets not only failed to disintegrate in the stomach but passed through the entire digestive tract practically unchanged. (Fig. 1.) Yet the label on this preparation read: "The special enteric coating protects the tablet from gastric secretions. It will disintegrate in the duodenum."

At the other extreme another brand of enteric-coated ammonium chloride tablets disintegrated in the stomach thus defaeting

FIG. 1. Roentgenogram showing shadows of the tablets in the colon which were not disintegrated.

the purpose of the coating. Disintegration of this brand within one hour of its ingestion is demonstrated in Figure 2. In addition, ammonium chloride was demonstrated chemically in the gastric contents.

After procuring descriptions of the methods used by pharmaceutical companies for testing their enteric-coated tablets *in vitro* we carried out similar tests in our laboratory.

Figure 3 shows three enteric-coated tablets of ammonium chloride; the three at the right are the original tablet before the test and the three on the left are tablets which had been placed in artificial gastric

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A B

FIG. 2. Roentgenograms of another product. A, immediately after ingestion; B, one hour after ingestion showing complete disintegration.

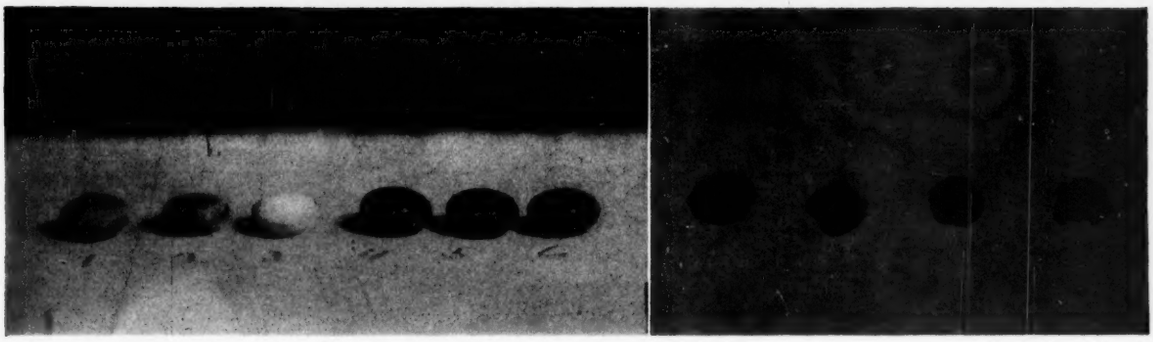
juice (formula of Toplis) at 38°C. for three hours, and in artificial intestinal juice (formula of Toplis) at 38°C. for four hours. The test showed that during the seven hours in the media the tablets retained 57 per cent of their original weight.

Figure 4 shows the results of our experiment with enteric-coated ammonium chloride tablets put out by another firm. These were placed in artificial gastric juice (formula of Toplis) at 38°C.; at the end of three hours all of the tablets were dissolved and only the coatings were left, despite the firm's claim that their enteric coating protects the drug from action of gastric juice and will break up in the intestines thus preventing gastric irritation.

After this experiment we found that the same thing holds true of enteric-coated digitalis, aminophylline and pancreatin. It was observed clinically that they, too, vary greatly in their disintegrating property, hence making the drug useless if it does not disintegrate at all and thereby depriving the patient of the needed remedy. The inefficacy of such drugs is only occasionally discovered in general practice.

Many pharmacologists are aware of the fact that the disintegration and the propulsion of enteric-coated tablets depends to a great extent on diet, the rapidity with which the stomach is habitually emptied, the degree of exercise and the degree of gastric acidity as well as upon other individual difference factors. However, the medical practitioner does not bear these facts in mind often enough.

We are particularly interested in calling attention to our experience with enteric-coated tablets for the following reasons: (1) No matter how reputable the pharmaceutical house it behooves the physician to watch carefully for the first forty-eight hours after administration of the drug to ascertain whether or not it has passed through the gastrointestinal tract without disintegrating. This is of particular importance when a drug such as digitalis is administered and when accurate maintenance doses are essential for the patient's well being. (2) There are some preparations on the market which



3 4

FIG. 3. Enteric-coated tablets of ammonium chloride: right, before *in vitro* test; left, after three hours in artificial gastric juice and four hours in artificial intestinal juice they still retain 57 per cent of their original weight.
FIG. 4. Enteric-coated tablets of ammonium chloride after *in vitro* test. After three hours in artificial gastric juice all tablets were dissolved and only the coatings were left.

in spite of being enteric-coated dissolve in the stomach. If the patient complains of gastric irritation following ingestion of the drug, it may be due to premature disintegration of the drug while still in the stomach. In many of these cases we found that simple vehicles used for the administration of ammonium chloride and other drugs are sometimes tolerated better by patients than when enteric coating is used.

SUMMARY

1. Investigations of enteric-coated drugs have shown that some with coatings which claim to "protect the tablet from gastric secretions" fail as well to disintegrate in any other part of the gastrointestinal tract.

2. Other preparations disintegrate in the stomach, and in these instances the enteric coating is of no particular value.

3. Clinically, all enteric-coated drugs when administered should be carefully watched for therapeutic effect.

REFERENCE

1. WORTON, A. G., KEMPF, G. F., BURRIN, P. L. and BIBBINS, F. E. New enteric coating and laboratory method for its control. *J. Am. Pharm. A.*, 27: 21–28, 1938.

Review

Status of Antithyroid Substances in Thyroid Disease*

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In clinical medicine the term "antithyroid substance" includes any agent capable of suppressing the formation of thyroid hormone by the thyroid gland. Among such materials are the thyroid hormone itself, iodine, certain thiocyanates, a number of other sulfur-containing compounds, particularly thioureas, thiouracils and sulfonamides and some aminobenzene derivatives devoid of sulfur, particularly *p*-, *m*- and *o*-aminobenzoic acid, *p*-aminophenylacetic acid and *p*-aminoacetanilide. Of these chemicals several are applicable at the bedside for control of conditions due to or associated with an overproduction of thyroid hormone, i.e., to all forms of thyrotoxicosis.

Administration of thyroid hormone to an individual who already has an excess will, it is true, decrease the output of hormone by the thyroid gland of the individual, but it will simultaneously maintain a high level of metabolic activity thus contributing little or nothing to the relief of the thyrotoxic manifestations.

Certain thiocyanates, particularly those of sodium and potassium, have been shown to interfere with the ability of the thyroid to trap iodine and thus with its overall capacity for the formation of iodothyroglobulin.[1–3] However, under certain conditions, particularly when the iodine intake is high, this action is uncertain and may be reversed, causing an aggravation of the thyrotoxic state already present. These thiocyanates are, therefore, not applicable to the treatment of patients with thyrotoxicosis.

The exact nature of the beneficial action of iodine in thyrotoxic states is far from clear. That it is capable of relieving, at least temporarily, many of the manifestations of hyperthyroidism in some but not in all patients there is no doubt. It has long been recognized that any agent normally taking part in an enzymic process will, if present in excess, interfere with the reaction. The doses of iodine usually used in the treatment of hyperthyroidism are from 150 to 600 times those normally made available to the thyroid gland. The actual processes through which this suppressive effect is accomplished have not been elucidated but it is clear from the work of Morton, Chaikoff and Rosenfeld[4] that the administered iodine becomes an active participant in the work of the thyroid cell under such conditions.

Inasmuch as the action of iodine alone is somewhat uncertain, it is now used mainly in an auxiliary or supplemental rôle and will be mentioned further in conjunction with other antithyroid compounds.

The antithyroid substances of most practical importance contain sulfur, held in combination by the radical $=N-\overset{\overset{S}{\|}}{C}-R$, in which R is usually —N= but in some instances may be —S— or —O—.[5] While preparations of the open chain type such as the thioureas are active, closed ring compounds, such as the barbituric acid derivatives and the thiouracils, are much more so.[6] For instance, propionylthiourea is but one-seventh as active as thiouracil.[6]

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CLINICAL COURSE OF REMISSIONS IN HYPERTHYROIDISM TREATED WITH THIOCARBAMIDE DERIVATIVES

The general pattern of action of all of the sulfur-containing antithyroid drugs thus far used in human beings for the treatment of all forms of thyrotoxicosis is quite similar. However, there are differences in the ease with which control is established, the time required to return the basal metabolism and blood protein-bound iodine to normal and the incidence and severity of toxic manifestations.

Under the influence of adequate doses of any of these compounds one to twelve weeks is the range of time necessary to bring the basal metabolic rate to normal, with an average of from three to five weeks. Subjective improvement usually occurs in from five to seven days. Nervousness is the first symptom to disappear in approximately one-half the patients.

As observed in 298 subjects, of which 193 had Graves' disease and 105 toxic nodular goiter, relief was first noted with the disappearance of one of the following manifestations, mentioned in the order of their frequency: apprehensiveness, insomnia, loss of weight, palpitation, systolic blood pressure above 150 mm. Hg and voracious appetite.

In the course of treatment toxic reactions may appear. These vary in frequency and severity depending upon the particular thiocarbamide derivative used. In the present studies an overall incidence of reactions to thiouracil occurred in approximately 13 per cent of all subjects, and to propylthiouracil in less than 0.5 per cent. Severe reactions necessitating the discontinuance of therapy included agranulocytosis, febrile urticarial reactions and jaundice (?). Complete agranulocytosis has been observed in about 2.5 per cent of all subjects given thiouracil and in none of those to whom propylthiouracil has been administered. Jaundice has been reported but the direct connection between its appearance and the use of a thiourea derivative has not been conclusively established. All fatalities have been attributed to either agranulocytosis or jaundice. Among the other toxic symptoms which may have called for an adjustment of dosage but not for the cessation of treatment have been headache, nausea, vomiting, swollen salivary and cervical glands, various types of rashes and edema of the ankles.

Following the complete control of the thyrotoxic state with an antithyroid drug, the systemic disturbances which remained in our patients were two-fold in nature: (1) permanent alterations in the thyroid, eye, heart and/or pancreas, directly traceable to the pre-existing thyrotoxicosis and (2) effects upon the thyroid and eye, possibly attributable to the treatment. It is with the second group that we are herein primarily concerned.

A decrease occurred in thirty-nine of 102 patients who initially showed exophthalmos. In three of these an aggravation of the condition has been observed. This has been relieved but not cured in two patients by the simultaneous use of maintenance doses of the antithyroid preparation, small doses of iodine (Lugol's solution, 1 minim daily or every other day) and varying amounts of desiccated thyroid substance (0.25 to 1.5 gr.) daily. In the third patient submaintenance doses of propylthiouracil have been employed and a mild thyrotoxic status allowed with a concomitant recession, but not remission, in the exophthalmic manifestations.

While under treatment with thiouracil,* 130 of 164 patients with initially enlarged glands were observed for variations in size. No actual measurements were attempted, but the impressions of the patient and his family and the independently recorded impressions of at least two observers were made the basis for the collection of the data. A decrease in size occurred toward the end of the first month of treatment in thirty-one

* Generous supplies of thiouracil and propylthiouracil have been made available through the courtesy of Dr. Stanton Hardy, Lederle Laboratories, Pearl River, N. Y.

of 103 patients with a Graves' type of disease, or toxic hyperplasia, and in twelve of sixty-one with a Plummer's syndrome, or toxic adenoma. At approximately three months in the former group and five months in the latter, twenty-four and twenty-one subjects, respectively, showed a definite increase in the size of the gland. No changes were observed in the configuration of the thyroid at any time in 42 of the 130 persons studied. Does the initial decrease in size correspond to the final "emptying out" of stored colloid and the later enlargement to hyperplasia "permitted" by the unopposed action of the thyroid-stimulating hormone of the pituitary?

In eighteen patients with enlarged thyroids, the toxicity of which has been controlled with propylthiouracil, we have concomitantly used a supplement of Lugol's solution, 1 minim daily. In three of these a further enlargement has been observed. This is a lower incidence than was observed in patients under treatment with thiouracil or propylthiouracil in whom iodine supplements were not used. The iodine supplement was begun as soon as the patient's basal metabolic rate was plus 20 per cent or below. It was continued until the thiocarbamide derivative was stopped although more or less arbitrarily the frequency of dose was often decreased to twice weekly for two or three months before it was completely omitted.

The group is too small for statistical analysis. However, there seems to be some justification for raising the question of the possible rôle of iodine as a useful adjunct in our management of hyperthyroidism with thiocarbamide derivatives. Calculated on a weight for weight basis the doses of iodine we have used correspond well to those in the rat which McGinty[7] has shown prevents the increase in weight produced by thiouracil. However, the amounts of thiouracil used by McGinty estimated on a similar basis were six or seven times those used in the human being. Nevertheless, it seems that his conclusions may hold for the thyrotoxic patient as well as for the normal rat, namely, that this action of iodine may be due not "to any toxic effect of iodide but to diminished sensitivity of the thyroid cells to thyrotropic stimulation." Astwood's observation[8] that sudden diminution took place in the size of the thyroid gland when iodine was administered in the course of thiouracil therapy is further confirmation in the human being of an action similar to that seen in the rat. Other observations by the same worker suggest that under some circumstances therapy with iodine and propylthiouracil may be factors in increasing the size of the thyroid.[9]

In preparation for surgery we use still larger doses of iodine, 250 to 375 mg. daily (30 to 45 minims of Lugol's solution), for periods up to three weeks without being able to detect any escape from the effects of the concomitantly employed thiouracil. Contrary to the practice of some of the larger clinics we continue thiouracil until the day before operation. That this does not interfere with the "colloid packing by iodine" is clearly shown in Figure 1, a microscopic section of the operative specimen removed from a man, forty-three years old, suffering from a Graves' type of goiter with a pretreatment basal metabolism of plus 73 and a preoperative value of plus 1. Undoubtedly a thyroid hormone-poor colloid with a high titer of iodine exists here as in the experimental animals subjected to nearly identical treatment with thiouracil and iodine.[7]

"PERMANENT" REMISSIONS FOLLOWING USE OF THIOURACIL AND PROPYLTHIOURACIL

The medical course of forty-three of seventy-one patients seen during the first year that thiouracil was available for our use has been followed to date. Fourteen are still under treatment. In the remaining twenty-nine (67.4 per cent) no drug has been administered for periods of from eighteen to thirty-seven months. It is believed that these can be looked upon as "cures." They are as likely to have recurrences, as other patients who have had

repeated bouts of thyrotoxicosis, whether operated upon or not.

Similar studies have not been completed in relation to treatment with propylthiouracil or for propylthiouracil in conjunction with iodine. However, the impression is gained from a preliminary review of available data that a small dose of iodine (8 mg. or less daily) added to the regimen after the thyrotoxic state is controlled may materially increase the number of permanent remissions.

INFLUENCE OF IODINE UPON THE ACTIVITY OF SULFUR-CONTAINING ANTITHYROID COMPOUNDS

The rôle of iodine in the management of thyrotoxicosis is not clear, nor is its effect upon the goitrogenic activity of sulfur-containing antithyroid compounds fully elucidated. Several points can be made: (1) A diet low in iodine markedly enhances the goitrogenic effect of thiouracil and similar compounds.[5,7] (2) When potassium iodide is added to the drinking water of thiouracil-treated rats in amounts ranging from 10 to 1,000 mg. per liter, there is slight inhibition of the goitrogenic effect but a rapid marked increase in the water-soluble iodine content of the thyroid gland.[5,7,10] Indeed, a single intraperitoneal dose of potassium iodide has caused the iodine concentration within the thyroid to return half way to normal within fifteen minutes. The amount of inorganic iodide thus trapped by the thiouracil-treated thyroid is roughly proportionate to the amount of iodine given. This iodine, however, remains in an inorganic form. (3) It is reported that pretreatment of thyrotoxic patients with large doses of iodine for periods varying from several days to several months slightly retarded onset of the inhibiting action of thiourea but increased its ultimate activity some threefold.[11–13] (4) Iodine in moderate dosage used concomitantly with thiouracil or some of its derivatives may decrease the frequency of relapses. (5) Excessive amounts of potassium iodide interfere with the synthesis of diiodotyrosine and thyroxin by the thyroid gland both *in vitro* and *in vivo*.[4]

No hard and fast conclusions can be drawn from these facts but some statements may be thought-provoking: (1) Sulfur-containing antithyroid compounds with the possible exception of the thiocyanates only partially prevent the trapping of iodine by the thyroid gland. (2) Pretreatment with moderately large doses of iodine delays the action of thiouracil and its closely allied goitrogens while small to moderately large doses do not influence an already fully established block to the formation of thyroid hormone. (3) Are the effects of iodine entirely related to its importance as a building material for thyroid hormone? This hardly seems likely in view of its capacity for inhibiting the formation of diiodotyrosine and thyroxin when present in excess. Moreover, doses which in toxic hyperplasia decrease the formation of hormone will, in simple iodine-deficiency goiter, increase the functional activity of the gland even to the point of causing thyrotoxicosis. Rawson et al.[14] and Danowski, Man and Winkler[12] believe the hyperplasia of thyrotoxicosis is reduced by iodine through its ability to inhibit the stimulating action of the thyrotropic hormone of the pituitary (TSH). Astwood[10] believes this action results not in decreased capacity of the pituitary for forming TSH but rather a depression of the action of TSH itself. (4) It seems likely that iodine in small doses should be used routinely in conjunction with thiouracil treatment of hyperthyroidism in an effort to determine an optimal dosage for the favorable influence that the combination has been shown to exert, at least in some cases and under some circumstances.

CHOICE OF ANTITHYROID DRUGS IN HYPERTHYROIDISM

Of more than 300 sulfur-containing compounds studied in animals[6,15–17] a little less than one-half have shown some detectable activity and twenty-five have proved to be active or more active than thiouracil.[17]

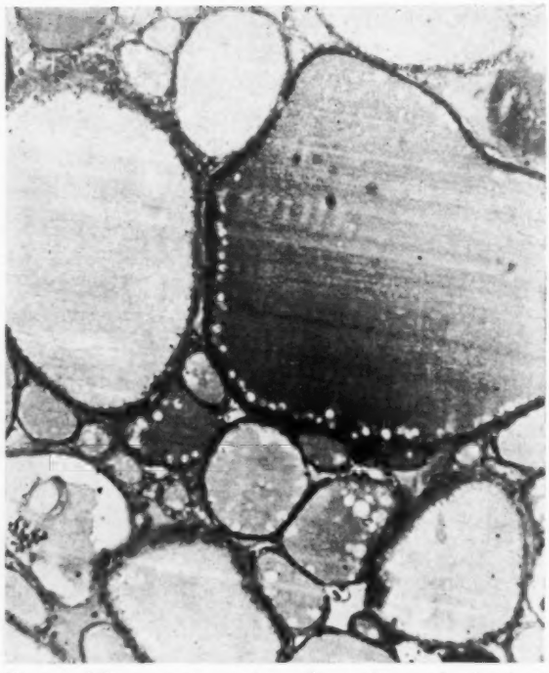

FIG. 1. Microscopic section of specimen obtained at operation (low power). A man, fifty-two years old, who first showed symptoms of Graves' disease without thyroid enlargement three months before he came under treatment. Prior to surgery the patient was treated for approximately eleven months with thiouracil and for seven months with propylthiouracil. The condition was fully controlled. However, the patient continued to have attacks of paroxysmal auricular tachycardia. Fifteen days prior to operation Lugol's solution, 15 minims three times a day, was added to the regimen. Note practically complete involution with large colloid lakes.

Of these twenty-five, five have come to clinical trial in the human being: 2-thiouracil, 6-methyl-2-thiouracil,[18–28] 6-ethyl-2-thiouracil,[5–29] 6-*n*-propyl-2-thiouracil[30–37] and 5, 5-diethyl-2-thiobarbituric acid (thiobarbital).[5,29,35,38,39] Four compounds, less active in the rat than thiouracil, have also been applied to the management of hyperthyroidism in human beings: thiourea,[11–13,20,27,28,40–56] tetramethyl-thiourea,[57] diethyl-thiourea[57] and 2-aminothiazole.[58–68]

The antithyroid activity of the nine substances just mentioned has been compared in rats and human beings. (Table I.) The activity index as determined in rats is that devised by McGinty and Bywater.[6] The activity in terms of thiouracil in human beings with thyrotoxicosis is derived from the average doses necessary to relieve the cardinal symptoms and signs of the disease and to normalize the basal metabolic rate and the protein-bound fraction of iodine in the blood. Thus, the activity index as described for human beings is far less accurate than that derived for the rat.

TABLE I
ACTIVITY INDEX OF ANTITHYROID COMPOUNDS

Substance	Activity Index (Thiouracil = 1.0)	
	Rats	Human Beings
Diethyl-thiourea	0.40	Too Toxic
Thiourea	0.10–0.12	0.3
2-Aminothiazole	0.15	1.0
Tetra-methyl-thiourea	0.30	1.0
2-Thiouracil	1.00	1.0
Thiourea plus iodine	.....	1.3
Thiobarbital	1.45	2.0
6-Methyl-2-thiouracil	1.15	2.0
6-*n*-Propyl-2-thiouracil	11.00	2.0–3.0
6-Ethyl-2-thiouracil	8.00	2.0–4.0

However, probably neither represents the total picture of the activity of any given compound for factors concerned with duration of action, dosage level at which activity is most pronounced, toxic manifestations, etc. are either partly or wholly neglected in such evaluation. Despite these shortcomings a fair clinical appraisal of the action of each drug can be reached.

In Figure 1 a comparison is made between the therapeutic effectiveness and the toxicity of the eight thiocarbamide derivatives which have been successfully used in human beings for the control of thyrotoxicosis. The only other drug of this group thus far employed in hyperthyroidism, diethyl thiourea, has been omitted from this illustration because of its toxicity. In each of the four patients upon whom it was tried severe toxic symptoms occurred when 0.6 Gm. were given daily;[57] however, such a dose was insufficient to relieve the manifestations of the coexisting thyrotoxicosis.[57]

The therapeutic activity of thiouracil has been placed at 1.0 and an attempt made to evaluate the usefulness of other drugs in terms of this arbitrary standard. (Fig. 2.)

In order to evaluate each drug fully some brief reference to the data of individual workers seems necessary.

Thiourea alone has been used in more than 375 patients[11–13,20,27,28,40–56] in initial daily doses ranging from 1.0 to 3.0 Gm., improves materially (Fig. 2) although the period of time necessary for control is somewhat lengthened. These workers observed remissions within from one to twelve weeks, with the majority occurring at about the fifth or sixth week of treatment. In

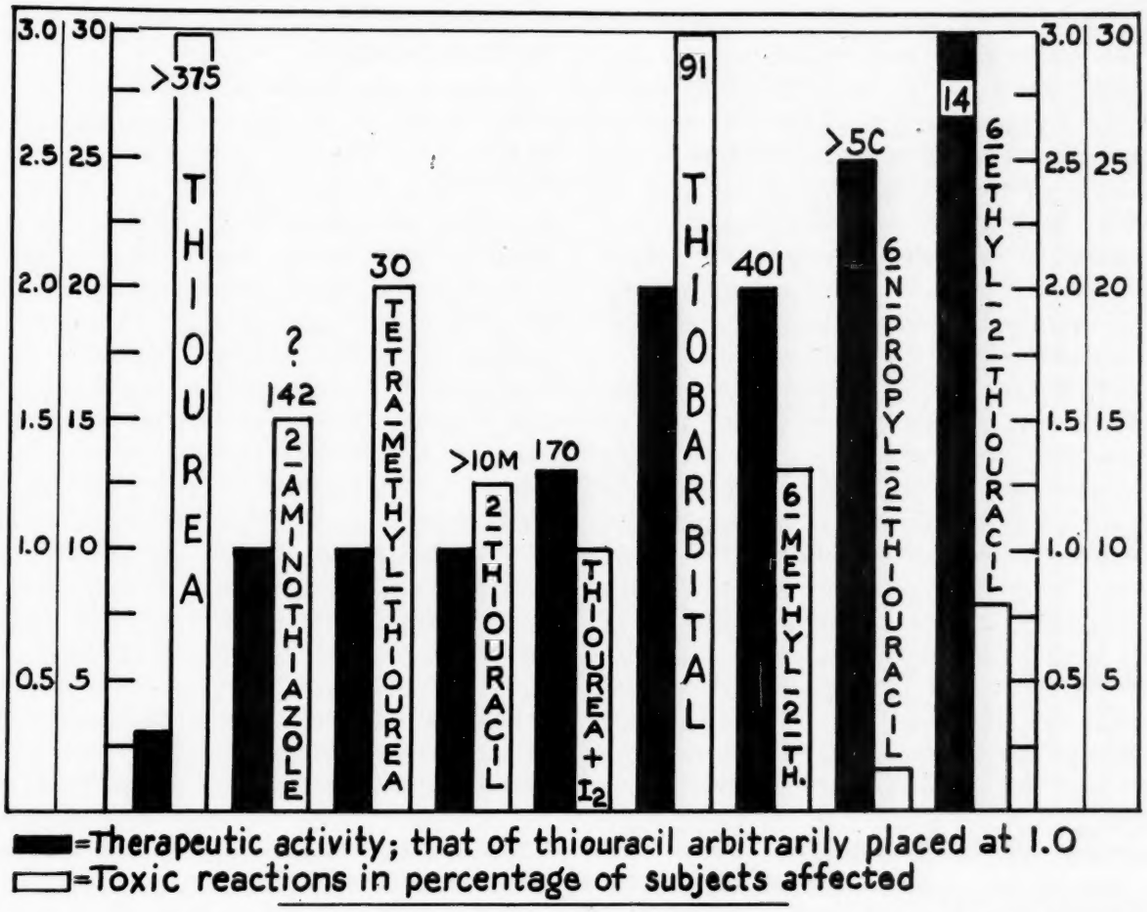

FIG. 2. A comparison of the therapeutic and toxic effects of antithyroid drugs in human beings. Numbers at top of each column represent number of subjects upon which data are based.

and maintenance doses from 0.3 to 1.0 Gm. On the average, it is approximately 0.3 as active as thiouracil. One worker reports "excellent results without toxicity" when from 0.25 to 0.60 Gm. of the drug are administered daily but gives no details of his investigations.[27] In the doses commonly employed the high toxicity (30 per cent) scarcely justifies further clinical trial. However, when the patient is pretreated or concomitantly treated with iodine, as has been done by one group of workers,[11–13] they claim that the efficiency of the drug their hands initial daily doses of thiourea have varied from 0.05 to 0.28 and maintenance doses from 0.025 to 0.08 Gm. In conjunction with this regimen strong tincture of iodine (U.S.P.) was employed in doses of 15 minims three times daily to yield approximately 440 mg. of iodine each twenty-four hours. As a rule, iodine is begun not less than one week prior to the initiation of the therapy with thiourea, and some patients reported by these investigators had received iodine for many months before the thiourea was added. As a result of their

experiences these workers recommend 0.11 Gm. of thiourea daily in divided doses in combination with the aforementioned dose of iodine, the regimen to be followed "indefinitely." They have observed remissions in 95 per cent of their patients but have seen relapses even after two years of treatment. Toxic symptoms due to the drug were uncommon and could usually be avoided by redistribution of the daily dose. While a careful review of the case reports made by them leaves some doubt as to the absence of toxic symptoms at the end of relatively long periods of treatment, the question of the value of combining iodine in some dose with the thiocarbamide regimen certainly warrants further consideration and study.

Tetramethylthiourea, despite a therapeutic activity only slightly lower than that of thiouracil, has proven too toxic to justify extensive clinical trial. In the doses first used (0.2 to 0.4 Gm. daily) the same statement holds true for thiobarbital.[29,39] However, in many instances control with thiobarbital can be attained by the use of 0.1 to 0.2 Gm. daily[38] and the drug has been tolerated in patients who developed reactions following use of thiouracil.[38] Perhaps more extensive trial is justified at a lower dosage level, particularly in view of its prolonged action and the rather high incidence of sustained remissions.[5,39]

Among one group of French workers, 2-aminothiazole has appeared to be a highly effective antithyroid compound, indeed approximately as effective, weight for weight, as thiouracil but 50 per cent more toxic.[59–62] However, opinion is sharply divided as other workers have discarded the drug as too toxic to justify further clinical trial.[58]

In the Scandinavian countries, and to a lesser extent in Australia, methylthiouracil has become the antithyroid drug most widely, in fact almost exclusively, used in the treatment of hyperthyroidism.[19–25,28] It is perhaps one of the most readily manufactured of the more highly efficient goitrogenic compounds. Initial doses have ranged from 0.06 to 0.90 Gm. daily with an approximate average of 0.2 Gm. daily. The necessary daily amount for maintenance of the patient in remission has varied from 0.01 to 0.30 Gm. with an average of 0.1 Gm. Weight for weight, therefore, the drug appears to be about twice as active as thiouracil although 25 per cent more toxic in effective dosages.

Astwood has made the only published study of results with 6-ethyl-2-thiouracil.[29] In fourteen patients he found the drug from two to four times as active as thiouracil and about three-fourths as toxic in effective dosage. Further trial seems to be justified.

Because of its low toxicity (approximately 0.5 per cent) and its high therapeutic activity (2.0 to 3.0), propylthiouracil is fast becoming the antithyroid drug of choice in this country. In this connection attention may well be called to the fact that the addition of any alkyl radicle at C_6 strikingly alters the efficiency of thiouracil. A number of the members of the methane series have thus been tried as a result of which it seems that maximum effectiveness appears when an ethyl radicle is used and a minimum toxicity is achieved with the propyl grouping.

Our own experiences with the antithyroid drugs center about thiouracil[69–72] and propylthiouracil.[30] The initial daily amount of thiouracil employed has varied from 0.6 to 0.8 Gm. with maintenance doses of 0.1 to 0.3 Gm. If 0.8 Gm. is initially used, this amount is decreased within seven days, irrespective of the clinical condition. If 0.6 Gm. is initially used, it is not continued for a longer period than two weeks when a reduction to 0.4 Gm. or less is made depending upon the status of the patient at that time.[70] With propylthiouracil, the initial dose now recommended lies between 0.20 to 0.25 Gm. daily. This may be continued in either instance until control is effected. Then a maintenance dose is established which in our experience has ranged from 0.025 to 0.150 Gm.[30]

In more than 200 patients to whom thiouracil has been administered we have failed to control the hyperthyroidism only in

those (eight in number) who have developed either an urticarial-febrile reaction or a complete agranulocytosis. On the other hand, three of one hundred patients have been difficult to maintain in a controlled state with prophylthiouracil; further adjustment of dosage may correct this difficulty, but we have the impression that the overall response may not be quite so dramatic as with thiouracil.

SUMMARY AND CONCLUSIONS

1. Eight sulfur-containing antithyroid compounds have been employed successfully for the control of thyrotoxic states of both the Graves' and Plummer's types: thiourea, 2-aminothiazole, tetra-methyl-thiourea, 2-thiouracil, 5, 5-diethyl-2-thiobarbituric acid, 6-methyl-2-thiouracil, thiourea plus iodine, 6-*n*-propyl-2-thiouracil and 6-ethylthiouracil. There is an increasing antithyroid effect in the order mentioned.

2. Thiourea, tetra-methyl-thiourea, thiobarbital, and probably 2-aminothiazole are probably too toxic in effective dosage to justify further clinical trials.

3. 6-*n*-propyl-2-thiouracil and 6-ethyl thiouracil appear to be the most promising members of the group thus far employed in human cases of hyperthyroidism.

4. Iodine in certain doses may enhance the degree of response to thiourea despite its retarding effect upon the rapidity of the action of that and all other drugs of this group.

5. Certain phases of antithyroid activity are discussed, particularly in relation to iodine intake.

REFERENCES

1. Wolff, J., Chaikoff, I. L., Taurog, A. and Rubin, L. The disturbance in iodine metabolism produced by thiocyanate: the mechanism of its goitrogenic action with radioactive iodine as indicator. *Endocrinology*, 39: 140, 1946.
2. Franklin, A. L., Chaikoff, I. L. and Lerner, S. R. The influence of goitrogenic substances on the conversion in vitro of inorganic iodide to thyroxin and diiodotyrosine by thyroid tissue with radioactive iodine as indicator. *J. Biol. Chem.*, 153: 151, 1944.
3. Vanderlaan, W. P. and Bissell, A. Effects of propylthiouracil and of potassium thiocyanate on the uptake of iodine by the thyroid gland of the rat. *Endocrinology*, 39: 157, 1946.
4. Morton, M. E., Chaikoff, I. L. and Rosenfeld, S. Inhibiting effect of inorganic iodine on the formation in vitro of thyroxin and diiodotyrosine in surviving thyroid tissue. *J. Biol. Chem.*, 154: 381, 1944.
5. Astwood, E. B. Chemotherapy of Hyperthyroidism. Harvey Lectures, 40: 195, 1944–45.
6. McGinty, D. A. and Bywater, W. G. Antithyroid studies. I. The goitrogenic activity of some thioureas, pyrimidines and miscellaneous compounds. *J. Pharmacol. & Exper. Therap.*, 84: 342, 1945.
7. McGinty, D. A. Conference on Thyroid Function as Disclosed by Newer Methods of Study. Iodine absorption and utilization under the influence of certain goitrogens. New York Academy of Sciences, Section on Biology. January 25, 1947.
8. Astwood, E. B. Chemotherapy in hyperthyroidism. *Surgery*, 16: 679, 1944.
9. Astwood, E. B. and Vanderlaan, W. P. Treatment of hyperthyroidism with propylthiouracil. *Ann. Int. Med.*, 25: 813, 1946.
10. Astwood, E. B. Mechanism of action of certain thyroid compounds. Conference on Thyroid Function as Disclosed by Newer Methods of Study. New York Academy of Sciences, Section on Biology. January 25, 1947.
11. Danowski, T. S., Man, E. B. and Winkler, A. W. Treatment of hyperthyroidism with a combination of iodine, thiourea in small doses, and desiccated thyroid. *Am. J. M. Sc.*, 210: 777, 1945.
12. Danowski, T. S., Man, E. B. and Winkler, A. W. The use of thiourea in the control of hyperthyroidism. *Connecticut M. J.*, 11: 105, 1947.
13. Winkler, A. W. and Danowski, T. S. Thiourea and related compounds in the treatment of hyperthyroidism. *Yale J. Biol. & Med.*, 18: 527, 1946.
14. Rawson, R. W., Moore, F. D., Peacock, W., Means, J. H., Cope, O. and Riddell, C. B. Effect of iodine on the thyroid gland in Graves' disease when given in conjunction with thiouracil —a two-action theory of iodine. *J. Clin. Investigation*, 24: 869, 1945.
15. Bywater, W. G., McGinty, D. A. and Jenesel, N. D. Antithyroid studies. II. The goitrogenic activity of some imidazoles and benzimidazoles. *J. Pharmacol. & Exper. Therap.*, 85: 14, 1945.
16. McGinty, D. A. and Bywater, W. G. Antithyroid studies. III. The goitrogenic activity of certain chemotherapeutically active sulfones and related compounds. *J. Pharmacol. & Exper. Therap.*, 85: 129, 1945.
17. Astwood, E. B., Bissell, A. and Hughes, A. M. Further studies on the chemical nature of compounds which inhibit the function of the thyroid gland. *Endocrinology*, 37: 456, 1945.
18. de Gasperis, A. Le thiouracil et le méthylthiouracil dans le traitement des thyrotoxicoses. *Minerva chir.*, 1: 43, 1946.
19. Leys, D. G. Hyperthyroidism treated with methyl thiouracil. *Lancet*, 1: 461, 1945.
20. Lundbaek, K. Toxic, allergic, and "myxedematoid" symptoms in the treatment of thyrotoxicosis with antithyroid substances (thiourea, thiouracil,

and methylthiouracil). *Acta. med. Scandinav.*, 124: 266, 1946.

21. Magnusson, P. and Sorensen, G. Treatment of hyperthyroidism with methylthiouracil. *Acta med. Scandinav.*, 125: 263, 1946.
22. Westergaard, J. Experiences in treatment of thyrotoxicosis with methylthiouracil. *Nord. med.*, 27: 1482, 1945.
23. Poate, H. R. G. Modern viewpoints in the treatment of thyreotoxicosis. *M. J. Australia*, 2: 789, 1946.
24. Poate, H. R. G. Methyl thiouracil in thyrotoxicosis. *M. J. Australia*, 2: 799, 1946.
25. Thyssen, J. Methylthiouracil therapy in thyrotoxicosis: preliminary report II. *Acta med. Scandinav.*, 121: 422, 1945.
26. Wilson, A. Thyrotoxicosis treated with thiouracil and methyl thiouracil. *Lancet*, 1: 640, 1946.
27. de Nogales, C. Thiouracil in hyperthyroidism. *Brit. M. J.*, 1: 365, 1946.
28. Poate, H. R. G. and Spencer, S. L. "Thio" drugs in thyreotoxicosis. *M. J. Australia*, 1: 493, 1946.
29. Astwood, E. B. Some new compounds for the treatment of hyperthyroidism. *Bull. New England M. Center*, 7: 202, 1945.
30. McGavack, T. H., Geri, A. J., Vogel, M. and Schutzer, S. A clinical comparison of the effectiveness of 6-n-propylthiouracil and 2-thiouracil as antithyrotoxic agents. *Am. J. Med.*, 2: 144, 1947.
31. Astwood, E. B. and Vanderlaan, W. P. Thiouracil derivatives of greater activity for the treatment of hyperthyroidism. *J. Clin. Endocrinol.*, 5: 424, 1945.
32. Astwood, E. B. and Vanderlaan, W. P. Propylthiouracil for hyperthyroidism. *Bull. New England M. Center*, 8: 143, 1946.
33. McCullagh, E. P., Ryan, E. J. and Schneider, R. Propyl thiouracil in the treatment of hyperthyroidism. *Cleveland Clin. Quart.*, 13: 232, 1946.
34. Crile, G., Jr. and Dinsmore, R. S. Present status of the surgical treatment of hyperthyroidism. *Cleveland Clin. Quart.*, 13: 50, 1946.
35. McCullagh, E. P. Present status of thiouracil. *Cleveland Clin. Quart.*, 13: 56, 1946.
36. Crile, G., Jr. Diagnostic clinic: diseases of the thyroid. *Post Grad. Med.*, 1: 51, 1947.
37. Watson, E. M. Treatment of toxic thyroid disease with thiouracil. *Edinburgh M. J.*, 53: 609, 1946.
38. Bartels, E. C. Thiobarbital in the treatment of hyperthyroidism. *J. A. M. A.*, 129: 932, 1945.
39. Astwood, E. B. Some observations in the use of thiobarbital as an antithyroid agent in the treatment of Graves' disease. *J. Clin. Endocrinol.*, 5: 345, 1945.
40. Astwood, E. B. Treatment of hyperthyroidism with thiourea and thiouracil. *J. A. M. A.*, 122: 78, 1943.
41. Beard, E. E. Thiourylene drugs in the treatment of hyperthyroidism. *Clin. Bull. Western Reserve Univ.*, 9: 13, 1945.
42. Campbell, D., Landgrebe, F. W. and Morgan, T. N. Pharmacology of thiourea. *Lancet*, 1: 630, 1944.
43. Cruz Coke, E., Rojas Mujica, G. and Diaz de Valdes, H. La thiourea y el thiouracilo en el hipertiroidismo. *Rev. méd. de Chile*, 73: 223, 1945.
44. Gibson, P. C. and Quinlan, J. T. Periarteritis nodosa in thiourea therapy. *Lancet*, 2: 108, 1945.
45. Goldsmith, E. D., Gordon, A. S., Finkelstein, G. and Charipper, H. A. A suggested therapy for the prevention of granulocytopenia induced by thiourea. *J. A. M. A.*, 125: 847, 1944.
46. Hendon, J. R. Observations on five cases of hyperthyroidism treated with thiourea derivatives. *Clinics*, 5: 727, 1946.
47. Himsworth, H. P. Thyrotoxicosis treated with thiourea. *Lancet*, 2: 465, 1943.
48. Horlick, L. Treatment of thyrotoxicosis with thiourea and thiouracil. *McGill M. J.*, 13: 121, 1944.
49. Maxwell, I. The treatment of thyrotoxicosis by thiourea, thiouracil and other drugs. *Roy. Melbourne Hosp. Clin. Rep.*, 15: 84, 1944.
50. Poate, H. R. G. A new treatment for thyreotoxicosis. *M. J. Australia*, 1: 163, 1944.
51. Ritchie, F. L. and Geddes, B. L. The use of thiourea in thyrotoxicosis; a report of 8 cases. *M. J. Australia*, 1: 381, 1944.
52. St. Johnston, C. R. Toxic reaction to thiourea: report on three cases. *Lancet*, 2: 42, 1944.
53. Williams, R. H. and Kay, G. A. Absorption, distribution, and excretion of thiourea. *Am. J. Physiol.*, 143: 715, 1945.
54. Netter, A. Les nouveaux traitements de l'hyperthyroïdie. *Progrès méd.*, 74: 120, 1946.
55. Himsworth, H. P. Discussion on thiouracil and thiourea in the treatment of thyrotoxicosis. *Proc. Roy. Soc. Med.*, 37: 693, 1944.
56. Paschkis, K. E., Cantarow, A., Rakoff, A. E., Walkling, A. A. and Tourish, W. J. Thiourea and thiouracil in treatment of thyrotoxicosis. *J. Clin. Endocrinol.*, 4: 179, 1944.
57. Williams, R. H. Antithyroid drugs: I. Tetramethylthiourea and diethylthiourea. *J. Clin. Endocrinol.*, 5: 210, 1945.
58. Himsworth, H. P. and Morgans, M. E. Aminothiazole in the treatment of thyrotoxicosis. *Lancet*, 1: 800, 1946.
59. Perrault, M. and Bovet, D. Aminothiazole in the treatment of thyrotoxicosis. *Lancet*, 1: 731, 1946.
60. Foreign Letter. *J. A. M. A.*, 132: 236, 1946. Treatment of hyperthyroidism with aminothiazole.
61. Foreign Letter. *J. A. M. A.*, 129: 761, 1945. Treatment of hyperthyroidism by aminothiazole.
62. Perrault, M. L'aminothiazol (2921 RP) dans le traitement de la maladie de Basedow. *Paris méd.*, 2: 401, 1946.
63. Perrault, M., Bovet, D. and Droguet, P. Chimiothérapie nouvelle des hyperthyréoses par l'aminothiazol (2921 RP). *Bull. et mém. Soc. méd. d. hôp. de Paris*, 60: 355, 1944.
64. Bastenie, P. A. and Tagnon, R. F. Traitement de l'hyperthyroidie par le thiouracil et par l'aminothiazol. *Acta clin. Belg.*, 1: 117, 1946.
65. Perrault, M. État actuel de la nouvelle chimiothérapie antithyroidienne par l'aminothiazol. *Semaine d. hôp. de Paris*, 21: 1071, 1945.
66. Perrault, M. and Bovet, D. Un antithyroidien nouveau: l'aminothiazol (2921 RP); résultats cliniques. *Ann. d'endocrinol.*, 6: 86, 1945.

67. Bovet, D., Bablet, J. and Fournel, J. Les bases expérimentales de la thérapeutique chimique des thyréotoxicoses par l'aminothiazol et les substances antithyroidiennes, *Semaine d. hôp. de Paris.*, 21: 1060, 1945.

68. Joliot, et al. Thyroïde, aminothiazole et iode radioactif. *Bull. et mém. Soc. méd. d hôp. de Paris*, 61: 213, 1945.

69. McGavack, T. H., Gerl, A. J., Vogel, M. and Schwimmer, D. The treatment of 26 thyrotoxic patients with thiouracil and a review of toxic reactions in all (135) reported cases. *J. Clin. Endocrinol.*, 4: 249, 1944.

70. McGavack, T. H., Gerl, A. J., Morton, J. H., Vogel, M. S. and Schwimmer, D. Observations on 78 thyrotoxic patients treated with thiouracil, *J. Clin. Endocrinol.*, 5: 259, 1945.

71. McGavack, T. H. and Drekter, I. J. The behavior of blood cholesterol in thyrotoxic patients under treatment with thiouracil. *J. Lab. & Clin. Med.*, 30: 586, 1945.

72. Rawson, R. W. and McArthur, J. W. What has thiouracil contributed to the management of Graves' disease? *New York State J. Med.*, 46: 2733, 1946.

Seminars on Protein Hydrolysates

Effect of Injury and Disease on Nitrogen Metabolism*

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A NORMAL full grown animal can be made to store excessive amounts of fat and carbohydrate as fat. Presumably it can utilize for the same purpose non-nitrogenous fractions of the amino acids, but it has no similar capacity to store the nitrogenous fractions of these compounds. Under ordinary circumstances the adult animal excretes daily as much nitrogen as it ingests. When the protein of the diet is increased, excretion of nitrogen in the urine for a brief interval falls short of the intake. This slight retention may represent only the amount required to accelerate the metabolism and excretion of nitrogen. Impairment of renal function may also cause temporary retention of nitrogen, not as protein, but as non-protein nitrogen. It has been generally accepted that a sustained positive nitrogen balance is evidence, and the only unequivocal evidence, that an adult animal has been depleted of protein. This is, of course, not true of the growing animal which retains nitrogen for the formation of new tissue. It is reasonable to assume also that hypertrophy of muscles and other organs must be attended by retention of nitrogen for the formation of protein. Recently it has been demonstrated that testosterone may promote economy in the use of protein. Under its influence the adult animal will store limited amounts of protein.[1]

When the quantity of protein in the diet is greatly diminished, the amount of nitrogen excreted falls accordingly with only a slight lag for a certain time. A point is ultimately reached, however, when the excretion falls less rapidly than the intake; the animal goes into negative nitrogen balance. As the reduction of protein is continued this loss of nitrogen increases but the actual quantity of nitrogen excreted diminishes. The catabolism of protein decreases to a minimum when an animal is receiving a diet that contains adequate calories but no protein.[2–5] With such diets the urinary nitrogen excretion of a human adult has been reduced to as little as 0.03 Gm. per Kg. per day, equivalent to 0.2 Gm. of protein.[2,5] Such low figures cannot be attained so long as the subject receives any protein, save possibly under circumstances that will be described later. The amount of protein required, both to maintain nitrogen equilibrium and to attain minimum nitrogen excretion, will depend upon the caloric value of the diets given. Body protein is used most conservatively when there is a generous supply of calories. A certain proportion of this must be supplied as carbohydrate but the major portion may be provided equally well as fat. Muscular activity does not appear to necessitate the expenditure of protein, provided a sufficient excess of carbohydrate and fat is given.[6,7] The calorigenic effect of thyroid can also be met with carbohydrate and fat.[3,4,8] The protein which is destroyed in the state of minimum nitrogen metabolism is apparently not spent for the production of energy.

The phenomena that attend deprivation of protein alone differ sharply from those that attend starvation. In the latter condition nitrogen excretion does not diminish to the same degree. At the end of thirty-one

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days Benedict's[9] fasting man was still excreting 7.2 Gm. of nitrogen, equivalent to 44 Gm. of protein, per day while after twenty-four days on a high calory diet containing less than 1 Gm. of nitrogen daily, Smith[5] excreted only 2.54 Gm. of N, equivalent to 16 Gm. of protein. This difference can be attributed partly to the lack of carbohydrate in the metabolism mixture of the starving subject. In the first three days after the period of starvation when Benedict's subject took only carbohydrate, the urinary nitrogen fell to 3.8 Gm. daily, a little more than one-half of what it had been during starvation. Presumably the extra protein is used for production of carbohydrate when this is not supplied in the diet. In another respect the nitrogen excretion of the starving subject differs from that of the person who subsists on a protein-free diet. The starving subject loses no nitrogen through the bowel because he does not defecate. Defecation does not cease nor does fecal nitrogen diminish to any great extent when protein is removed from the diet. During the control period, on a diet containing 13 Gm. of nitrogen, Smith excreted 1 Gm. daily in his feces. During the twenty-four days in which his diet contained an average of only 0.65 Gm. of nitrogen the feces contained an average of 0.82 Gm. per day.

When the quantity of protein in the diet is altered, the various nitrogenous components in the urine do not change proportionally. Urea and ammonia, especially the former, are most affected; the other compounds in the urine change very little. In the course of twenty-four days the urea nitrogen in Smith's urine fell from 10.20 to 0.32 Gm. per day, or 97 per cent; ammonia nitrogen from 0.50 to 0.20, or 60 per cent while the remaining nitrogen diminished from 0.151 to 0.112 Gm., only 26 per cent. Urinary urea and ammonia are the most completely oxidized products of protein metabolism. They may be regarded as representative of the protein that has been utilized for the production of energy. Creatinine, uric acid and the other compounds that make up the remainder of urinary nitrogen appear to have more specific and indispensable purposes.

Minimum protein metabolism Folin termed endogenous metabolism, which he conceived as the result of irreducible wear and tear of the proteins of the body. It seemed to be implied in this concept that the streams of endogenous and exogenous protein metabolism were distinct. Except for the small fraction that was used to replace the quantities worn out by the endogenous processes, the exogenous protein was diverted to combustion. From the gross standpoint of overall accounting this concept is unimpeachable; from the standpoint of the individual components of the diet it is altogether untenable. Schoenheimer[10] by means of amino acids tagged with heavy isotopes showed that the products of exogenous protein become inextricably mixed with endogenous compounds. Not only are fragments of amino acids exchanged but proteins appear to pick up amino acids from their environment. The isotopic technic has also greatly advanced knowledge of the specific functions of amino acids. Besides their general function in the formation of various types of proteins, certain fractions of the amino acids are used for formation of nitrogenous compounds that are required for the conduct of special metabolic processes. It has been discovered that certain of the amino acids must be supplied from extraneous sources while others can be synthesized in the body.

Of the amino acids found in the body nine are now recognized as essential, i.e., beyond the synthetic capacity of animals.[11] These are: threonine, valine, leucine, isoleucine, lysine, phenylalanine, tryptophane, histidine and methionine. Arginine should probably be added to this group. It is apparently synthesized but not with sufficient facility to meet the requirements.[11] These amino acids have been termed essential because they must be supplied preformed in the diet. In a broader sense, however, all amino acids are indispensable, some more directly than others. Cystine

and tyrosine can be synthesized only from the essential amino acids methionine and phenylalanine, respectively. Consequently, if cystine and tyrosine are not provided preformed, sufficient excess of methionine and phenylalanine must be supplied to yield the necessary amounts of cystine and tyrosine. An animal given a diet that contains an adequate amount of protein that is deficient with respect to one or more of the essential amino acids fails to grow, loses weight and ultimately succumbs. It wastes nitrogen throughout this process of deterioration. Such deficiencies may be absolute or relative. If the protein is not altogether devoid of any essential acid, the deficiency may be overcome by administration of large enough quantities of the protein to provide adequate amounts of the amino acid. It is impossible under these circumstances to achieve any economy in the use of protein. Among the features that determine the nutritive efficiency of a protein are the proportions of the various amino acids of which it is composed. The optimum proportions for growth and maintenance have been only roughly ascertained.

It is becoming evident that deficiencies might arise from endogenous as well as dietary causes. Disorders or diseases may interfere with proper utilization of an amino acid for an essential purpose, for example, the formation of cystine from methionine, or may create an unusually large demand for some particular derivative of one of the amino acids, for example, the methyl group of methionine. The existence of such deficiencies, while not conclusively demonstrated, is tacitly implied in the use of cystine and methionine for the treatment of disorders of the liver, nephrosis, etc.

It has been stated that minimum protein metabolism can be attained only if an animal is given large amounts of fat and carbohydrate with no protein. Millard Smith,[5] after twenty-four days on a diet containing less than 1.0 Gm. of nitrogen daily, had lost 94 Gm. of nitrogen, or 590 Gm. of protein. In spite of this, when he was given a regular diet at the end of the period, his nitrogen excretion rose from less than 3 Gm. per day to about 8 Gm. In the course of this experiment Smith's protein stores had been only moderately depleted. He could still be regarded as a well nourished individual. When an animal has been reduced to a state of severe malnutrition by deprivation of protein, it can apparently utilize protein with greater efficiency.[12–14] The growing animal seems to be able to achieve a similar economy.[3]

Although a sustained positive nitrogen balance is accepted as practical proof of previous protein depletion, failure to establish a positive balance does not exclude antecedent protein depletion. In fact, *per se*, it gives no precise information about the past. It may indicate, as has been previously mentioned, that the subject is receiving too few calories or protein that is deficient in quantity or quality. On the other hand, it may indicate that the subject is suffering from some one of the many disorders that give rise to the condition long known as "toxic destruction of protein." As much as sixty years ago (Shaffer and Coleman)[1] Friedrich Müller showed that patients with typhoid fever lost comparatively large quantities of nitrogen in the urine. The phenomenon was carefully studied by Shaffer and Coleman,[15] Kocher,[16] DuBois and associates[17–20] and others. Subsequently, it has been found that similar destruction of protein follows acute hemorrhage,[21,22] operations and injuries[23–26] and a variety of other conditions.

Kocher[16] showed that a normal person subsisting on a diet containing minimal amounts of protein, but high calories, could perform heavy muscular work without any increase of urinary nitrogen, but the nitrogen excretion of patients with febrile diseases could not be reduced to a minimum by similar diets. DuBois and associates[17–20] could not prevent losses of nitrogen in such conditions by administration of diets containing adequate amounts of protein and calories far in excess of the needs of the patients. The degree and duration of the de-

struction of protein seem to vary with the severity of the injury or disease[16–20,26,27] if the term "severity" is loosely defined. The critical features that determine the uneconomical use of protein have not yet been identified. Nitrogen losses can be prevented without difficulty after the repair of inguinal hernias but not after appendectomies. Negative nitrogen balances regularly follow major fractures but nitrogen equilibrium is easily established after osteotomies.[27,28] Grossman et al.[27] found that in meningococcus meningitis and in scarlet fever, treated by sulfonamide drugs, negative nitrogen balances frequently continued despite high protein diets, after the temperature had become normal and symptoms and signs of the disease had been abolished. The losses of nitrogen appeared to be related to the inherent gravity of the disease, not to its clinical manifestations. It is evident from these observations and studies of fractures[28] that fever is not responsible for the wastage of protein.

Protein is used in this profligate manner after injury only by previously healthy persons. Moreover, this reaction to injury appears to be self-terminative. After it has continued for a certain length of time the los of nitrogen gradually diminishes. Ultimately, provided that an adequate diet is given, a positive nitrogen balance can be established, even if the disease or injury continues. Shaffer and Coleman[15] and Coleman and DuBois[17] established positive nitrogen balances during relapses in three of their patients with typhoid fever, although they had been unsuccessful in the earlier stages of the disease. If they can be made to eat, patients with tuberculosis[29] and other chronic infections[27] will store protein. Browne and associates[30] have suggested that the early stage in which protein is wasted should be termed the catabolic phase of injury, the later stage in which protein is stored the anabolic phase. They found that during the anabolic phase renewed injury caused little waste of nitrogen.

Shaffer and Coleman[15] were unable in most instances to prevent losses of nitrogen during the early stages of typhoid fever. They were, however, able to influence these losses by varying the caloric value of the diets they gave. Nitrogen excretion was distinctly greater when the diets contained less than 2,000 calories than it was when the diets contained 3,500 or more calories. The losses of protein were not inversely proportional to the calories given but when the caloric intakes fell below the daily energy requirements extra protein was expended. The protein-sparing effect of calories has also been demonstrated by Brunschwig et al.[24]

Whether or not wastage of protein after injury can be mitigated or abolished by dietary measures has been a subject of controversy. Differences of opinion can undoubtedly be attributed partly to failure to recognize the conditioning features which have been previously mentioned. It is obvious that in the analysis of data both the severity and duration of the injury must be considered. In the studies of typhoid fever by Shaffer and Coleman,[15] for example, it is impossible in most instances to decide whether a change of nitrogen metabolism is referable to dietary regulation or to the course of the disease. In none of the earlier experiments by Coleman, DuBois, etc.[1,3–5] were positive nitrogen balances established in the most acute stages of the diseases studied. The quantities of protein employed by these investigators, however, were not large according to present standards although they were deemed extremely generous in an era in which protein in disease had a noxious reputation. Attempts to give these quantities were often thwarted by anorexia and digestive disturbances. The effect of feeding large quantities of protein was not, therefore, subjected to rigorous examination. With a more tolerant attitude toward protein and with concentrated preparations of easily assimilable and highly nutritious proteins, it became possible to reopen the investigation in a less restricted manner. The obstacle of anorexia was removed by the development

of hydrolysates of protein suitable for intravenous administration.

With these aids, Grossman et al.[27] were quite unable to establish nitrogen equilibrium even with large amounts of protein and high calories in patients with severe acute infections or after serious injuries or operations. Howard,[26,28] Browne[30] and their associates were equally unsuccessful. By giving large quantities of mixtures of amino acids or hydrolysates of protein Madden and Clay[31] produced positive nitrogen balances in a certain proportion of dogs with sterile abscesses induced by injections of turpentine. Such lesions are, however, relatively trivial and of short duration. Hirschfeld and his associates,[32] by giving 150 or more Gm. of protein and over 4,000 calories per day, succeeded in establishing positive nitrogen balances almost from the beginning of treatment in some burned patients, but they failed in others. The same inconsistency is evident in the series of cases presented by Elman[33] and by Brunschwig et al.[24] In Elman's series some of the patients were obviously chronically ill and wasted. In all cases an interval of four to six days elapsed between the injury and administration of protein hydrolysates. This is the period in which the greatest losses of nitrogen have been observed.[24,27] The success of Mulholland, Co Tui et al.[25] in conserving protein after gastrectomy by means of protein hydrolysates may have been referable to the fact that these operations were performed chiefly on chronically wasted patients. For similar reasons many other reports must be discounted. Studies of persons with large exudative lesions must also be rejected unless the quantities of nitrogen lost in the exudates are measured. This criticism applies to the positive balances reported by Cope and associates[33] in burned persons.

Cuthbertson[23] found that nitrogen excretion immediately after operation was not great but became considerable after three or four days. This was confirmed by Grossman,[27] Peters and associates[34] and by Howard[26] after fractures. This increase may be apparent rather than real; it may be related only to the protein intake which is minimal immediately after an operation or severe injury. When Grossman et al.[27] gave protein hydrolysates equivalent to 75 Gm. of protein intravenously on the first two postoperative days, the negative nitrogen balances did not differ appreciably from those of patients who received no protein. The extra nitrogen from the hydrolysates was apparently wasted in the urine. In Shaffer and Coleman's[15] cases of typhoid, negative nitrogen balances seldom exceeded 12 Gm. daily at the height of fever. In only one case, in which attempts at feeding were ineffectual, was the negative balance extremely large. In this instance the excessive waste of protein may be attributed to deficient calories. Injury appears to provoke no malicious destruction of protein but to compel the expenditure of a certain amount of tissue protein. Insufficient calories will increase these losses but administration of extra protein does not seem to diminish them. Whether by administration of extremely large quantities of protein and calories the native protein can be spared is still a debatable question.

If this disorder is an inevitable reaction to injury, it may be of no advantage to try to correct it, at least immediately after operation. Hirschfeld, Abbott et al.[32] did, in fact, find that early administration of large amounts of protein to burned patients provoked nausea, vomiting, diarrhea and other untoward symptoms. After the first few days, however, patients were able to take large quantities of protein without deleterious effects. Since the reaction to injury is self-terminative and its duration unpredictable, generous amounts of protein should be given early enough to anticipate the anabolic phase; generous calories should be provided as early as possible to minimize the losses of body protein. The impression has been voiced that high protein diets improve the sense of well being and hasten the appearance of the anabolic phase. Such impressions are hard to evaluate. There can be no doubt that high protein

diets accelerate the restoration of body protein once the anabolic phase has begun. The patient who is suffering from chronic diseases or incurs an acute injury while in a state of debilitation deserves high protein and calories from the start because he can use protein efficiently.

It has been suggested that acute injury or disease creates a specific need for extra amounts of some particular amino acid. Croft and Peters[35] by administering methionine to rats diminished the nitrogen losses after thermal burns. This reaction cannot be related directly to the injury since methionine has been shown to promote economy of protein in normal animals.[36] If the wastage of nitrogen after injury were an expression of the need for extra amounts of some particular amino acid, it should respond more readily to administration of large quantities of protein containing this acid. The partition of nitrogen in the urine does not suggest that protein metabolism is being diverted into abnormal channels. After injury the usual proportion of urinary nitrogen is excreted as urea plus ammonia. Additional dietary nitrogen appears entirely in these forms.[1,2,14,34] The non-urea nitrogen of the urine does not vary with the nitrogen in the diet. The excretions of creatinine[1,2,34] and of uric acid[1,2] are also not consistently affected.

The reaction to injury manifests itself in certain other disturbances that have been less generally recognized. Cuthbertson and Tompsett[37] reported that immediately after operations the concentration of protein in the serum fell rapidly. This observation was verified by Peters[34] who found that only the albumin fraction of the proteins suffered. This drop, Man[34] showed, was accompanied by a similar reduction of serum lipids in which all fractions of the lipids participated. Hypo-albuminemia and hypolipemia in disease have been generally attributed to malnutrition. Although it appears to be well established that serum albumin does fall when an animal is deprived of protein, it is quite clear that current opinions about the general clinical significance of hypo-albuminemia must be revised. The precipitate fall of serum albumin after operation cannot be attributed to general depletion of protein. If it were due to malnutrition, it should decline throughout the catabolic phase as nitrogen wastage progresses, but it may even rise appreciably in the face of large negative nitrogen balances.[34]

Man[38] found that during the catabolic phase of the injury reaction the concentration of α-amino acids in the serum was usually low, even if the subjects were receiving high protein diets and had large negative nitrogen balances. This was contrary to expectation. It had been anticipated that the amino acids of the serum would reflect the rate of turnover of protein. It was further discovered that, like serum albumin and lipids, amino acid nitrogen fell sharply after operations. It had already been found that it was low in certain infectious diseases[39] and in the abdominal crises of the nephrotic syndrome.[40]

These phenomena appear to be an integral part of the reaction to injury. Like the wastage of body protein the reductions of serum albumin, lipids and amino acids appear only in patients who were previously in a healthy condition. In patients debilitated by chronic disease these components of the serum, usually already low, do not fall further or fall only slightly after an operation. In healthy persons the extent of their decline varies with the gravity of the operative procedure. The explanation and significance of these phenomena has not been elucidated. What useful purpose they may possibly serve is not apparent. Injury seems to dislocate the metabolic processes profoundly. The disturbance is characterized by impairment of the synthesis of protein, including serum albumin and a tendency to route products of protein metabolism preferentially to urea and ammonia.

Since protein is an essential constituent of tissues that cannot be replaced by other foodstuffs, its loss is presumably disadvantageous and should be prevented. Until, however, the nature of the disorder has been

discovered a certain amount of wasting with attendant delay of convalescence and rehabilitation may have to be accepted as an inevitable consequence of severe injuries. Every effort should be made to minimize the losses of protein. In chronic debilitating conditions since the synthetic powers of the body appear to be intact, administration of generous quantities of protein with adequate calories should be a major therapeutic objective. This is equally true in acute pathologic states after the catabolic phase has ended. Since this phase is self-terminative and of variable duration, administration of generous diets should not be delayed until its termination. The anabolic phase should be anticipated. There is no evidence that administration of large amounts of protein during the catabolic phase is injurious. An exception may have to be made of the two or three days immediately following operation. Even if patients cannot be prevented from losing protein during the catabolic phase, the extent of these losses can be reduced to a minimum by administration of large quantities of carbohydrate and fat.

The development of protein hydrolysates suitable for intravenous injection has been a great achievement. With the aid of such preparations, it has at last become possible to administer protein to patients who are unable to eat. It appears to have been established beyond reasonable doubt that nitrogen equilibrium can be maintained and that the protein requirements of normal animals and men can be satisfied by means of properly prepared hydrolysates of efficient proteins. There is, however, no evidence that intravenous injection of such preparations is superior from a nutritive standpoint to the normal method of eating. In fact, all evidence favors the ingestion of whole protein. If hydrolysates are not injected at an extremely slow rate, they provoke nausea and vomiting. In this respect mixtures of pure amino acids might have distinct advantages because, according to Madden and associates,[41] they can be injected in high concentration with great rapidity without provoking untoward reactions. It would also be possible to vary such mixtures to meet special nutritive requirements. No preparations of pure amino acids suitable for such purposes are, however, commercially available. The slow rate of injection required for hydrolysates limits the amount of protein that can be provided in this form. It also necessitates administration of undesirably large quantities of fluid. In order to administer the equivalent of 75 Gm. of protein with the usual commercial hydrolysates it is necessary to inject 2,000 cc. of fluid over a period of at least four hours. In addition to the protein hydrolysate this fluid usually contains 100 Gm. of glucose, a quantity incapable of supplying the calories required for the day. The total value of such a mixture is only 700 calories. This may be raised to 1,100 calories by using a 10 per cent instead of a 5 per cent glucose solution as diluent; it may be supplemented by additional injections of 10 per cent glucose. Seldom, however, is it possible by these methods to give more than 75 Gm. of protein and 300 to 400 Gm. of glucose, a total of 1,500 to 1,900 calories per day. In order to achieve this the patient must be subjected to a tedious and distressing procedure.

It has been proposed that parenteral hydrolysates be given as supplements to the diets of patients who are able to eat but cannot or will not take enough for their needs. For this purpose such injections are peculiarly unsuitable. The nauseating effects of hydrolysates when given too rapidly have already been mentioned. Even if they are given slowly enough to avoid nausea, patients cannot be induced to eat while they are being injected. Since the injections take so long, they cannot be given during the day without interfering with meals. They must, therefore, be delayed until the evening, thereby interfering with much needed rest.

On the whole, if a patient has no disorder of the gastrointestinal tract that prevents ingestion and utilization of food, it is usually possible to administer more protein and calories by mouth than can be given solely

by parenteral means or with the aid of parenteral supplements. This requires, however, resourcefulness and attention to detail that are seldom given to the subject. This is one of the chief reasons for the excessive use of parenteral feeding; once the needle is inserted the day's ration runs in without much attention. Moreover, the ration comes prepared and packaged so no thought is given to its composition. Diets must be selected with consideration of their nutritive value and the tastes and strength of the patient. It is not uncommon to see a patient staring at a tray, not because he lacks appetite but because he lacks strength and energy to wrestle with the food. Frequently when the tray is taken away, it contains only those foods that demanded effort on his part. Some will eat only if they are fed, others only if the diet is so prepared that it requires no implements other than the hands and a spoon. Unhappily there is a tradition that diets of this kind must be bland, a euphemism for insipid. Lack of physical strength does not necessarily connote disability of the digestive functions. Furthermore, the physical taste and appearance of food are no criteria of their actions in the gastrointestinal tract. Patients who are refused any highly tasty food are frequently given without thought vile tasting or aromatic medications.

In a certain proportion of subjects it is necessary to resort to fluid feedings chiefly or entirely. With the aid of prepared foods, and especially powdered milk, it is possible to make fluid diets highly nutritious and especially rich in protein. When fluid diets are prescribed, advantage should be taken of the sense of thirst as well as the need for nutrition. A full water pitcher need not always be at the bedside. Something more nutritious may be used to allay the desire for fluid. Thirst can even be stimulated by the judicious use of salty fluids if there is no contraindication to the use of salt.

No justification can be found for oral administration of protein hydrolysates, whether it be by ordinary processes of ingestion or by tube. Co Tui[42] contends that such preparations are more easily utilized than undigested proteins but this claim is not supported by physiologic observations. Most hydrolysates are so distasteful that oral administration is impracticable. If it were possible to devise less unpleasant preparations, they would still be undesirable. Despite Co Tui's claims, investigations have disclosed that excretion of nitrogen in the feces is greater when hydrolysates are given than when whole proteins are given.[43] In fact, some hydrolysates, if given in anything approaching adequate proportions, provoke diarrhea. The reasons for this have not been thoroughly investigated and are not germane to this discussion. It is a general rule that processes of secretion and absorption in the gut are not separable.

One useful application of intravenous hydrolysates is worth mentioning. It is well established that complete starvation inhibits the activities of the gastrointestinal tract and the digestive secretory glands. The starving man has no bowel movements.[9,44] So long, at least, as there is no obstruction of the alimentary canal, gastrointestinal activity can be abolished by starvation even in the face of severe irritative or inflammatory processes. Under these conditions, however, neither food nor fluids must be introduced into the stomach or gut whereas the normal starving man can apparently take water without inducing bowel movements. In acute mercury poisoning, vomiting and diarrhea cease after a brief interval if the patient is permitted to take nothing by mouth.[45] If vomiting and diarrhea do not cease upon withdrawal of food and fluids, a local or generalized peritonitis should be suspected (unpublished). Apparently parenteral administration of fluids, including protein hydrolysates, does not provoke gastrointestinal activity. It provides a means, therefore, of preventing or mitigating wasting while starvation and deprivation of fluids are employed to abolish activity of the alimentary tract,

either in preparation for operation or as a means of checking diarrhea.

REFERENCES

1. Kenyon, A. T., Knowlton, K., Sandiford, I., Koch, F. C. and Lotwin, G. A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism. *Endocrinology*, 26: 26, 1940.
2. Deuel, H. J., Jr., Sandiford, I., Sandiford, K. and Boothby, W. M. A study of the nitrogen minimum. The effect of sixty-three days of a protein-free diet on the nitrogen partition products in the urine and on the heat production. *J. Biol. Chem.*, 76: 391, 1928.
3. Krauss, E. Untersuchungen über den minimalen Eiweissverbrauch des Menschen unter gesunden und krankhaften Bedingungen. *Deutsches Arch. f. klin. Med.*, 150: 13, 1926.
4. Lauter, S. and Jenke, M. Über den Eiweisstoffwechsel bei verschiedenen Krankheiten (Versuche über das N-Minimum bei Diabetes, Carcinom, Leukämie, Bestrahlung, Thyreotoxikose (Basedow), Pneumonie.) *Deutsches Arch. f. klin. Med.*, 146: 323, 1925.
5. Smith, M. The minimum endogenous nitrogen metabolism. *J. Biol. Chem.*, 68: 15, 1926.
6. Campbell, J. A. and Webster, T. A. Day and night urine during complete rest, laboratory routine, light muscular work and oxygen administration. *Biochem. J.*, 15: 660, 1921.
7. Wilson, D. W., Long, W. L., Thompson, H. C. and Thurlow, S. Changes in the composition of the urine after muscular exercise. *J. Biol. Chem.*, 65: 755, 1925.
8. Boothby, W. M., Sandiford, I., Sandiford, K. and Slosse, J. The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects. I. A method studying the reserve or deposit protein with a preliminary report of the results obtained. *Ergebn. d. Physiol.*, 24: 728, 1925.
9. Benedict, F. G. A study of prolonged fasting. Carnegie Institute of Washington, 1915. Publication No. 203.
10. Schoenheimer, R. The dynamic state of body constituents. Cambridge, 1942. Harvard University Press.
11. Rose, W. C. The nutritive significance of the amino acids. *Physiol. Rev.*, 18: 109, 1938.
12. Hindhede, M. Studien über Eiweissminimum. *Skandinav. Arch. f. Physiol.*, 30: 97, 1913.
13. Hoesslin, H. von. Klinische Eigentümlichkeiten und Ernährung bei schwerer Inanition. *Arch. Hyg.*, 88: 147, 1919.
14. Kestner, O. Der Eiweissumsatz des Menschen. *Ztschr. f. physiol. Chem.*, 130: 208, 1923.
15. Shaffer, P. A. and Coleman, W. Protein metabolism in typhoid fever. *Arch. Int. Med.*, 4: 538, 1909.
16. Kocher, R. A. Uber die Grösse der Eiweisszerfalls bei Fieber und bei Arbeitsleistung. Untersuchungen mittels des Stickstoffminimums. *Deutsches Arch. f. klin. Med.*, 115: 82, 1914.
17. Coleman, W. and DuBois, E. F. Clinical calorimetry. VII. Calorimetric observations on the metabolism of typhoid patients with and without food. *Arch. Int. Med.*, 15: 887, 1915.
18. Barr, D. P. and DuBois, E. F. Clinical calorimetry. XXVIII. The metabolism in malarial fever. *Arch. Int. Med.*, 21: 627, 1918.
19. Cecil, R. L., Barr, D. P. and DuBois, E. F. Clinical calorimetry. XXXI. Observations on the metabolism of arthritis. *Arch. Int. Med.*, 29: 583, 1922.
20. Coleman, W., Barr, D. P. and DuBois, E. F. Clinical calorimetry. XXX. Metabolism in erysipelas. *Arch. Int. Med.*, 29: 567, 1922.
21. Buell, M. V. Studies of blood regeneration. II. Effect of hemorrhage on nitrogen metabolism. *J. Biol. Chem.*, 40: 63, 1919.
22. Endres, G. and Neuhaus, C. Austauschvorgänge zwischen Gewebe und Blut. I. Die Wirkung des Aderlasses auf die Blutgase und das Säurebasengleichgewicht des Organismus. *Ztschr. f. d. ges. exper. Med.*, 47: 585, 1925.
23. Cuthbertson, D. P. Observations on the disturbance of metabolism produced by injury to the limbs. *Quart. J. Med.*, 1: 233, 1932.
24. Brunschwig, A., Clark, D. E. and Corbin, N. Postoperative nitrogen loss and studies on parenteral nitrogen nutrition by means of casein digest. *Ann. Surg.*, 115: 1091, 1942.
25. Mulholland, J. H., Co Tui, Wright, A. M. and Vinci, V. J. Nitrogen metabolism, caloric intake and weight loss in postoperative convalescence. *Ann. Surg.*, 117: 512, 1943.
26. Howard, J. E., Parson, W., Stein, K. E., Eisenberg, H. and Reidt, V. Studies on fracture convalescence. I. Nitrogen metabolism after fracture and skeletal operations in healthy males. *Bull. Johns Hopkins Hosp.*, 75: 156, 1944.
27. Grossman, C. M., Sappington, T. S., Burrows, B. A., Lavietes, P. H. and Peters, J. P. Nitrogen metabolism in acute infections. *J. Clin. Investigation*, 24: 523, 1945.
28. Howard, J. E., Winternitz, J., Parson, W., Bigham, R. S., Jr. and Eisenberg, H. Studies on fracture convalescence. II. The influence of diet on post-traumatic nitrogen deficit exhibited by fracture patients. *Bull. Johns Hopkins Hosp.*, 75: 209, 1944.
29. McCann, W. S. The protein requirement in tuberculosis. *Arch. Int. Med.*, 29: 33, 1922.
30. Browne, J. S. L., Schenker, V. and Stevenson, J. A. F. Some metabolic aspects of damage and convalescence. *J. Clin. Investigation*, 23: 932, 1944.
31. Madden, S. C. and Clay, W. A. Protein metabolism and protein reserves during acute sterile inflammation. *J. Exper. Med.*, 82: 65, 1945.
32. Hirschfeld, J. W., Abbot, W. E., Pilling, M. A., Heller, C. G., Meyer, F. L., Williams, H. H., Richards, A. J. and Obi, R. Metabolic alterations following thermal burns. III. Effect of variation in food intake on nitrogen balance of burned patients. *Arch. Surg.*, 50: 194, 1945.
33. Cope, O., Nathanson, I. T., Rourke, G. M. and Wilson, H. Metabolic observations. *Ann. Surg.*, 117: 937, 1943.

34. Peters, J. P. Nitrogen metabolism in acute and chronic disease. *Ann. New York Acad. Sc.*, 47: 327, 1946.
35. Croft, P. B. and Peters, R. A. Nitrogen loss after thermal burns. Effects of adding protein and methionine to diet of rats. *Lancet*, 1: 266, 1945.
36. Allison, J. B., Anderson, J. A. and Seeley, R. D. The determination of the nitrogen balance index in normal and hypoproteinemic dogs. *Ann. New York Acad. Sc.*, 47: 245, 1946.
37. Cuthbertson, D. P. and Tompsett, S. L. Note on effect of injury on level of plasma proteins. *Brit. J. Exper. Path.*, 16: 471, 1935.
38. Man, E. B., Bettcher, P. G., Cameron, C. M. and Peters, J. P. Plasma α-amino acid nitrogen and serum lipids of surgical patients. *J. Clin. Investigation*, 25: 701, 1946.
39. Farr, L. E., McCarthy, W. C. and Francis, T., Jr. Plasma amino-acid levels in health and in measles, scarlet fever and pneumonia. *Am. J. M. Sc.*, 203: 668, 1942.
40. Farr, L. E. The intravenous administration of small doses of casein hydrolysate to nephrotic children and its effect upon the nitrogen balance and plasma amino acid level. *J. Pediat.*, 16: 679, 1940.
41. Madden, S. C., Carter, J. R., Kattus, A. A., Jr., Miller, L. L. and Whipple, G. H. Ten amino acids essential for plasma protein production effective orally or intravenously. *J. Exper. Med.*, 77: 277, 1943.
42. Co Tui. Clinical experiences with oral use of protein hydrolysates. *Ann. New York Acad. Sc.*, 47: 359, 1946.
43. Riegel, C., Koop, C. E., Drew, J., Stevens, L. W. and Rhoads, J. E. The nutritional requirements for nitrogen balance in surgical patients during the early postoperative period. *J. Clin. Investigation*, 26: 18, 1947.
44. Winkler, A. W., Danowski, T. S., Elkinton, J. R. and Peters, J. P. Electrolyte and fluid studies during water deprivation and starvation in human subjects, and the effect of ingestion of fish, of carbohydrate, and of salt solutions. *J. Clin. Investigation*, 23: 807, 1944.
45. Peters, J. P., Eisenman, A. J. and Kydd, D. M. Mercury poisoning. *Am. J. M. Sc.*, 185: 149, 1933.

Conference on Therapy

Management of Disorders of Cardiac Rhythm

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. J. JAMES SMITH: The internist and the cardiologist spend a good deal of time on the subject which is to be discussed in this conference, namely, the management of disorders of cardiac rhythm. The opening remarks will be made by Dr. Gold.

DR. HARRY GOLD: I should like to suggest that we consider the treatment of disorders of cardiac rhythm under three separate headings: First, there is the treatment of the patient with a chronic or persistent disorder of rhythm, for example, the case of persistent auricular fibrillation or flutter or heart block. Second, there is the problem of the acute attack of disordered rhythm such as the paroxysm of auricular fibrillation, auricular flutter, auricular tachycardia, ventricular tachycardia or heart block. The third problem is the prevention of recurrences of attacks in patients with paroxysmal disorders of rhythm.

The problems of therapy are quite different in these three categories. For example, in the patient with chronic auricular fibrillation one rarely aims at abolishing the abnormal rhythm. One usually tries merely to slow the ventricular rate to normal levels and to allow the patient to carry on with the auricles in fibrillation. In the second category the patients present themselves in the midst of an attack of disordered rhythm, an attack of auricular fibrillation. They may give a history of having had previous attacks but, whether they do or not, the problem before you at the time is that of abolishing fibrillation of the auricles and restoring a normal rhythm. In the third category the patients present themselves with a normal rhythm but are seeking advice because of repeated attacks of disordered rhythm of one kind or another. The immediate therapeutic problem in these situations is not that of abolishing an attack but of devising a system which will prevent recurrences of whatever kind of attacks the patient is suffering. Obviously these three categories of the problem are not mutually exclusive and in many instances one may be confronted with the matter of not only abolishing the attack that is present at the time but of preventing recurrences in the same person.

I am sure that you are all familiar with the common disorders of rhythm but I list them here to make it easier to discuss them: (1) premature contractions; (2) auricular paroxysmal tachycardia; (3) auricular flutter; (4) auricular fibrillation; (5) ventricular tachycardia; (6) heart block.

It is a matter of the greatest importance to establish the precise diagnosis and to recognize which one of these disorders of rhythm is the presenting problem. When the differential diagnosis is made, it is the unusual case in which one will fail to bring the abnormal rhythm under control by appropriate application of one or another specific drug. In most cases it is fairly easy to establish the precise abnormal mechanism, but there are patients in whom the differential diagnosis is a matter of the greatest difficulty and defies solution even in the hands of the most expert and with the aid of all the special diagnostic devices.

We shall not have the time here to go into the details of differential diagnosis. If we try that, we shall certainly have no time left for a discussion of treatment. What I

should like to do in the two minutes that remain for my introductory remarks is to point out what I believe to be the best procedure in the case of a patient presenting a paroxysm of rapid heart action, whether it be regular or irregular, and in which we do not have the means for establishing the precise abnormal mechanism at work. Specifically, assume that a patient presents himself to you with an attack of rapid heart action, regular or irregular, and suppose that with the methods available at the time, you cannot determine whether the problem is one of frequent premature contractions, auricular tachycardia, auricular flutter, auricular fibrillation or ventricular tachycardia. This is a situation in which the general practitioner finds himself not infrequently. Now assume that you wish to terminate the abnormal rhythm. What should you do? What treatment would provide the best chance of bringing the abnormal rhythm under control without appreciable risk? My suggestion is the use of quinidine. Give the patient 0.6 Gm. (10 gr.) of quinidine sulfate every two hours and examine the heart before each dose. Continue the medication until the attack comes to an end or until the patient develops symptoms of intolerance such as those of cinchonism (blurred vision, tinnitus and impaired hearing) or gastrointestinal symptoms (nausea, vomiting and diarrhea). These minor toxic effects preclude further use of the drug. The two-hour interval is chosen because the maximum effect of any one dose usually develops in this period of time. If the first dose has caused no minor toxic effects, the next dose of 10 gr. is not likely to produce any serious effects. The object is to build the effects of one dose on the effects of the previous one until a level is reached in the body sufficient to terminate the abnormal rhythm. Here is one drug which provides a good chance of bringing under control a fairly large proportion of the patients with any one of five different disorders of cardiac rhythm.

Of course, we are much better off if we are in a position to establish the exact nature of the abnormal rhythm before treatment is started. That is so because quinidine is not the best choice for all of these five disorders. For example, an intravenous injection of 3 U.S.P. units of an appropriate digitalis preparation, such as ouabain, cedilanid or digoxin, repeated in fifteen to thirty minutes if necessary, may terminate a paroxysm of auricular tachycardia within a few minutes and it may do so with complete safety, whereas oral doses of quinidine may take hours to achieve the same result and the intravenous injection of quinidine is risky except in the hands of those who have had a good deal of experience with its use in that way. I will ask you to bear in mind that the suggestion which I have made concerning the use of quinidine applies only in those circumstances in which the patient has developed an ectopic rhythm and in which for one reason or another the precise nature of the ectopic rhythm is not determined. I hope that the discussion will make clear the best measures for patients in whom the contrary is true, namely, in those instances in which the precise nature of the disordered rhythm is established.

DR. SMITH: Dr. Stewart, would you care to take up the discussion at this time?

DR. HAROLD J. STEWART: Those of us who see a large number of patients with paroxysmal disorders of rhythm find that nodal tachycardia is the most common disorder. This and auricular paroxysmal tachycardia are grouped under the term supraventricular tachycardia. The two are treated similarly.

I was amazed to hear that a paroxysm of auricular fibrillation would need to be treated without a clinical diagnosis. Most of these patients have such a rapid ventricular rate that a large pulse deficit results and the physician should be able to make a correct diagnosis. In auricular flutter one often sees the flutter waves in the neck veins when the patient lies flat and the veins fill up. The examiner is often able to estimate the ratio of the number of flutter waves to the number of ventricular

beats. In paroxysmal auricular tachycardia the rhythm is regular and the rate is constant while in ventricular tachycardia one can hear a little whirr which indicates a slight irregularity, and every now and then a large wave is seen in the jugular vein in the neck when the auricles and ventricles contract simultaneously. In short the physician ought to be able to arrive at a diagnosis in many cases of paroxysmal disorders of rhythm without electrocardiographic aid before treatment is started. Good medical practice requires under most circumstances that one should know what the condition is before one treats it. Many physicians have portable electrocardiographic machines and carry them along when they see a patient in whom there is the emergency of an abnormal rhythm.

I agree that if one does not know the nature of the paroxysm, quinidine may be used with the greatest safety. It is not likely to do any harm in several of the disorders of rhythm whereas digitalis could do harm if the rhythm proved to be ventricular tachycardia.

When the precise nature of the abnormal rhythm is known, the measures which may be used are fairly specific. For a paroxysm of auricular or nodal tachycardia digitalis is, in our experience, more effective than quinidine. First, it is well to try simple measures, such as having the patient take a deep breath and hold it, the Valsalva experiment or have the patient gag himself; if the patient is not too ill, nausea may be induced; these measures will frequently terminate an attack. If these are not effective, carotid sinus pressure may be applied; but in this case atropine ought to be at hand in case the carotid pressure causes prolonged cardiac asystole. The carotid pressure is applied first on one side, then on the other and finally on both sides simultaneously if necessary. We have seen attacks terminated by the additive effect of carotid sinus pressure while the patient is taking a deep breath. Occasionally we use mecholyl subcutaneously in doses of 20 to 30 mg. in young individuals and 30 to 50 mg. in older individuals. Here also, atropine ought to be at hand before mecholyl is given, and it should be injected at once if the patient shows any idiosyncrasy to the mecholyl. Mecholyl is a dangerous drug. It causes many side effects and we do not use it very often. Occasionally we use apomorphine or ipecac to induce vomiting. Finally, if these measures have not proved effective, the patient is digitalized. This usually terminates the paroxysm promptly. One drug should not be used in paroxysmal auricular tachycardia is morphine; if the patient has recurrent attacks, morphine addiction may result.

In auricular flutter we have also found digitalis most effective. It is our practice to digitalize the patient, and it is our experience that it may take more than the usual therapeutic dose of this drug to restore the normal rhythm. If digitalis proves ineffectual after a suitable trial, quinidine may be tried and in a few instances this will restore the normal rhythm.

It is our experience that in many cases of paroxysmal auricular fibrillation with rapid ventricular rate the abnormal rhythm ceases spontaneously when the patient is put at rest and kept quiet. If, however, the abnormal rhythm persists and its prompt termination is indicated, we usually give digitalis to slow the ventricular rate. The normal rhythm might then return, but in the event that the auricular fibrillation still continues, quinidine may be used to terminate it.

The students should be reminded that complete heart block and bundle branch block are contraindications to the use of quinidine.

Dr. Smith: For several days I have been trying to find someone who has had some experience with intravenous procaine in disorders of cardiac rhythm. It has been like trying to find a man who has voted in a Gallup poll. It seems as though the anesthetists are one jump ahead of us in this matter. I hope we may have some discussion on that subject.

Dr. Pardee, would you care to make some remarks?

DR. HAROLD E. B. PARDEE: I agree with Dr. Stewart in the matter of diagnosis. I should dislike to think of a situation in which one could not make the differential diagnosis between auricular fibrillation and a paroxysm of auricular tachycardia. All one has to do is to listen to the beat of the heart; one beat is totally irregular and the other is perfectly regular. The rate in a paroxysm of auricular fibrillation may be rapid, perhaps 180 per minute, but as one listens carefully one perceives phases in which the rhythm falters. That does not occur in a paroxysm of auricular tachycardia.

Dr. Stewart referred to variations in the rhythm of patients with ventricular tachycardia. In my experience this irregularity seems to be much talked about but rarely seen in the records. Slight irregularity is occasionally seen in the rhythm of ventricular tachycardia but it is certainly not a characteristic of this disorder.

I want to say a word about carotid pressure, not as a method for treatment but as a method for diagnosis. Carotid pressure is very useful in diagnosis. In auricular flutter, carotid pressure will usually slow the heart, especially if the patient has not had quinidine in amounts sufficient to block the vagal mechanism.

The technic of carotid pressure should be carefully performed. It is not enough to press on the carotid artery. Unless it is properly done, the carotid sheath is merely pushed behind the larynx and the pressure is not effective. If one uses the thumb and presses the artery back against the muscle mass of the vertebral column, one is more likely to secure an effective stimulus. This should be done first on one side and then on the other. Sometimes the pressure on one side, sometimes on the other will terminate a paroxysm of auricular tachycardia. In the case of auricular flutter, carotid pressure does not result in cessation of the flutter but in a marked slowing of the rhythm for a few beats.

Something should be said about the advisability of giving quinidine to patients in whom an attack of auricular fibrillation has persisted for some days. As Dr. Gold has suggested, one should hesitate to use quinidine in auricular fibrillation of long duration. After a certain time, particularly if heart failure has developed, thrombi appear in the auricles and these may become emboli when the auricles begin to contract with restoration of normal rhythm. It is, of course, true that the same occurs in patients who spontaneously return to normal rhythm but then one cannot help that. In a patient in whom an attack of auricular fibrillation has lasted for forty-eight hours it is inadvisable to use quinidine. In such a case it is best to use digitalis first in sufficient amounts to slow the ventricular rate to the normal range, allowing fibrillation of the auricles to continue.

A word about the paroxysm of ventricular tachycardia. This is the most difficult paroxysm to terminate. It often resists the various measures to which other tachycardias respond. Quinidine in adequate doses should be the first choice. Magnesium sulfate is sometimes useful in ventricular tachycardia. An intravenous dose of 20 cc. of a 10 or 20 per cent solution of magnesium sulfate will sometimes terminate an attack of ventricular tachycardia when other measures have failed.

DR. CARY EGGLESTON: Virtually all the effective and useful measures for controlling the paroxysmal disorders of rhythm have already been mentioned. In the light of Dr. Gold's opening remarks I may draw attention to the fact that in the majority of cases the situation is not one of grave urgency. Of course, it is our desire always to give the patient relief as promptly as possible but, within the range of my experience, there is time in most instances to analyze the patient's condition fairly thoroughly and to determine the precise nature of the mechanism involved.

I think the greatest problem is presented by those patients who come to the doctor with a history of recurrent attacks of severe palpitation. By questioning these patients

one will sometimes unearth a history that permits one to hazard a diagnosis as to the probable mechanism with reasonable accuracy. Statistics are helpful in this regard. We know that the auricular form is far more common than any other form of paroxysmal tachycardia. It gives rise to a regular rhythm. The patient is usually able to sense the difference between regular and irregular rhythm. Our major problem lies in the group in which the patients seek relief from possible future attacks and in which we lack adequate information for a precise diagnosis. As Dr. Stewart has mentioned, I also think that digitalis is very effective in the control of auricular paroxysmal tachycardia; it is less effective in the nodal form. However, I agree with Dr. Gold's opening remarks that in a case in which the diagnosis cannot be made with certainty we should probably resort to quinidine.

I mentioned the fact that in the majority of cases the paroxysms of abnormal rhythms do not present urgent problems, but there are times when the situation is one of immediate urgency. For example, the patient may black out, as he calls it, in these attacks. In my experience I find that this reaction is more likely to occur at the onset or possibly at the termination of an attack than at any other time. In many cases we just have to take our chances and try quinidine. We inform the patient that it is imperative to have an electrocardiogram made at the time of the next attack, no matter what the circumstances, whether it be during the day or night, whether the patient be near or far from the office. The patient should be urged to get to the office, a hospital or a laboratory and have an electrocardiogram taken at once. I might add that one cannot always be certain of the diagnosis even with an electrocardiogram although it is usually most helpful. Once the diagnosis is established one can select rational therapy.

I would like to add to the remarks made on carotid sinus pressure. It is wise to have the patient lying down during carotid sinus pressure because every once in awhile this procedure will cause syncope. I agree with Dr. Pardee's comments on the technic. I have seen a good many patients in whom the so-called carotid sinus pressure was tried without avail because it was so imperfectly carried out.

Use of digitalis to terminate an attack of auricular tachycardia has already been mentioned. This drug is also useful in preventing recurrences. We can very often carry the patient along satisfactorily for protracted periods of time by the use of fairly large doses of digitalis. We have one patient attending our clinic here who used to be incapacitated by these attacks and now comes in merely for a routine check, with the statement that the paroxysms of auricular tachycardia are only occasional, very brief and not particularly troublesome.

The danger of emboli resulting from the termination of paroxysms of auricular fibrillation has been mentioned. I have not seen any serious embolic phenomena under these conditions. This merely may be a difference of experience in the case of two men. I highly respect Dr. Pardee's opinion in this matter. It has been frequently emphasized that it is inadvisable to terminate a paroxysm of auricular fibrillation by means of quinidine if it has endured for any considerable length of time. Perhaps it is merely good fortune on my part but I have never seen a disaster from bringing such an attack to an end.

Dr. Smith: It might be pointed out that carotid sinus pressure produces its effect as the result of a reflex stimulation of the motor vagal fibers to the heart. The same result, namely, a stimulus passing down the motor fibers of the vagus to the heart, may be obtained in many other ways, such as deep inspiration, straining, pressure on the eyeballs, pulling out of the tongue or more noxious forms of stimulation. Some of these may be more successful than pressure on the carotid sinus.

Dr. Deitrick, when Dr. Gold mentioned the administration of 0.6 Gm. of quinidine every two hours, I saw a cloud cross your face. I think you were concerned with the

question as to what Dr. Gold would do when he encountered a case in which the quinidine caused cardiac standstill. Would you care to join the discussion at this point?

DR. JOHN B. DEITRICK: It is perhaps unfortunate, although in a conference like this it is unavoidable, that discussion of the treatment of disorders of rhythm is divorced from a consideration of the underlying disease processes which bring them about. I am sure you all will agree that the management of these patients is not merely a problem of juggling a few drugs.

Dr. Gold stated that the first thing to do, in the event of a paroxysm of abnormal rhythm in which the precise mechanism cannot be ascertained, is to give the patient quinidine. May I state that I would do in such a case? First, I would endeavor to determine whether or not the patient had an abnormal rhythm. Then I would try the simple devices of carotid sinus pressure, gagging, bending the head forward between the knees and simple eyeball pressure. The next thing I would do would be to give the patient a dose of morphine. Dr. Stewart stated that he would not give morphine because if the patient had repeated attacks it might lead to addiction. In my experience with many patients I find that my worries are over after I have administered morphine. The patient with a paroxysm of auricular tachycardia is usually apprehensive and ill at ease. He is disturbed by a feeling of vigorous pounding within the chest. Not infrequently a dose of 10 or 15 mg. of morphine solves the problem before one even has had an opportunity to try out the more specific drugs to abolish the attack. The third thing I would do would be to give quinidine and in this I agree with Dr. Gold.

I was curious to know how much of a problem the abnormalities of rhythm present and so we examined the matter at Bellevue Hospital. We found that there were 181 cases of abnormal rhythms in the hospital last year. The total was broken down into the following: 122 with auricular fibrillation; eighteen with nodal rhythm; five with supraventricular tachycardia; fourteen with auricular flutter; twelve with paroxysmal auricular tachycardia and ten with ventricular tachycardia. You will note that we had practically the same number of cases of nodal rhythm as of auricular flutter.

In connection with the comments on abolishing auricular fibrillation I am inclined to think that the danger has been overemphasized. There are two points to be considered here, namely, the danger of emboli and the fact that in some cases the restored normal rhythm does not continue. We had a patient this year in whom the fibrillation had been present for nearly two weeks; in this instance quinidine restored a normal rhythm uneventfully. This patient had no valvular disease and the heart was not markedly enlarged. I agree with Dr. Stewart's findings to the effect that patients are better off with a normal rhythm than with auricular fibrillation. Even though digitalization controls the ventricular rate in auricular fibrillation, the cardiac output is not as good as when the same patient has a normal sinus rhythm. I believe that we should try to restore a normal rhythm in these patients more often than we do. There is not sufficient time here to consider all the criteria for placing patients in the category of those in whom the attempt to restore a normal rhythm should be made.

There are figures indicating that the incidence of emboli is higher in patients with auricular fibrillation lasting a year or more than in those in whom a normal rhythm is restored. The evidence, however, is not conclusive because there may have been selection of patients, and those in whom the auricular fibrillation persisted may have been patients with a more advanced disease.

Dr. Smith referred to the recent case in which an attempt to abolish a paroxysm of ventricular tachycardia resulted in a complete auricular standstill. This occurred after about 2.5 Gm. of quinidine had been given. Yet, according to Dr. Gold, that is not an excessive amount of quinidine. It

was given in fractions at intervals of two hours.

DR. GOLD: Was that 0.6 Gm. every two hours?

DR. DEITRICK: Yes, and the patient developed a complete auricular standstill. This was temporary and was followed by restoration of a normal rhythm.

I might add one word about nodal tachycardia. I find it very difficult to control. Some of you may recall the patient here at New York Hospital last year and the difficulties encountered in his management. I wonder whether there is any better treatment than digitalis to terminate a paroxysm of nodal tachycardia. I would like to ask Dr. Gold whether quinidine has any effect on the A-V node.

DR. SMITH: Dr. Gold, maybe you are going to answer my question on procaine.

DR. GOLD: I have had no direct experience with it, but there is good experimental evidence showing that procaine has a quinidine-like action on the myocardium so that one might expect results similar to quinidine. There is the question of its dangers and that point has not been sufficiently established. Dr. Burstein published a report in the March, 1946 issue of *Anesthesiology* in which he found 30 to 70 mg. of procaine injected intravenously effective in abolishing various ectopic rhythms occurring in the course of thoracic surgery. There is the fact that these patients were anesthetized, and such doses of procaine may be safer in anesthetized individuals than in others. We need more experience in relation to the dosage of procaine. It seems to me quite worth while to pursue observations on procaine in this connection.

I think this a proper time to discuss the various comments which have been made on my opening remarks. I am glad to see that there is no disagreement with my general thesis, namely, that quinidine is the drug of choice in all of five disorders of cardiac rhythm under certain conditions. Those conditions are (1) the particular case in which a decision has been reached that normal rhythm should be restored as quickly as possible and (2) the case in which the differential diagnosis with respect to the precise mechanism at work has not been made. The failure to establish the precise mechanism may be due to several factors; either the available facilities are not adequate, the physician is a general practitioner without sufficient experience to enable him to differentiate them or the physician is an expert in these matters, but in spite of all the measures for differential diagnosis is still unable to arrive at a precise diagnosis.

Most of the comments which appear to be in disagreement relate to a matter which I had hoped would be omitted in this conference, namely, differential diagnosis, in order to allow us time to explore more fully the items of treatment. Obviously, that would require certain assumptions, namely, that the diagnosis had been established or that a final decision concerning the diagnosis cannot be reached. Dr. Stewart indicated that the differential diagnosis between these disorders of rhythm is easy to make, and he expressed amazement that one would be unable to establish the diagnosis of a paroxysm of auricular fibrillation, auricular flutter and auricular tachycardia by clinical means. I must admit that an expert will arrive at a fairly sound hunch within a few minutes by means of the electrocardiogram and carotid sinus pressure. But I must also add that the expert who has carefully analyzed both his successes and failures in differential diagnosis will not feel particularly secure in his decision in a great many cases. Dr. Deitrick's reference to the 181 cases at Bellevue Hospital last year is of interest in this connection: In this series five cases were labeled "supraventricular tachycardia." What is the meaning of such a diagnosis? Does it not mean that in nearly 3 per cent of the cases they were unable to decide what ectopic rhythm the patient had? The term "supraventricular tachycardia" is commonly applied to an abnormal rhythm in which the electrocardiogram shows an essentially normal ventricular complex, but in which one cannot determine the nature

of the auricular activity. When one can determine it, one does not use a term which indicates merely that the pacemaker is somewhere above the ventricle, but labels the condition sinus tachycardia, auricular tachycardia, nodal tachycardia or auricular flutter. As Dr. Eggleston stated, the most rational and most effective treatment is possible only when these precise diagnoses are made. Here then is the failure to make the exact diagnosis in one of every ten cases with a regular abnormal rhythm in the hands of experts in an outstanding hospital with all the facilities for establishing the diagnosis. Consider, therefore, how much worse the situation may be in the case of the country doctor who may have no electrocardiograph, or may be less familiar with carotid sinus pressure during the taking of the electrocardiogram, as well as with the special features of the tracing which enable one to distinguish several of these disorders of rhythm.

In my opening remarks I described the treatment which is best under these conditions. The plea for establishing the mechanism of abnormal rhythm is, to be sure, quite proper. I should be the last one to recommend the treatment of disorders of cardiac rhythm without at least an attempt at a precise diagnosis, but I have had enough experience to make me aware of the rather wide gap between an attempt and success in this problem. What I wished to emphasize was the fact that in a large proportion of these cases the patient does not have to go without specific and effective treatment even though a precise diagnosis is not made.

I agree with Dr. Eggleston that many of these paroxysms of ectopic rhythm do not present urgent situations and every effort should be made to establish the precise mechanism, not only for the purpose of using the most effective method of treatment for the current attack but also to prevent repetitions. One can, of course, argue that if the situation is not urgent and the diagnosis cannot be made, one should merely sit by until the attack subsides spontaneously. It is very likely to do so after minutes or hours or days in the majority of cases. In fact, most patients present themselves with a history of previous attacks which did subside spontaneously and that is the meaning of the term paroxysmal ectopic rhythm. We must leave it to the judgment of the physician to decide whether it is important or imperative to terminate the attack as quickly as possible. As Dr. Eggleston pointed out, these attacks sometimes give rise to a "blackout." There are other urgent problems. Some patients who never had anginal symptoms before will develop a severe attack of substernal pain radiating to both arms, wrists and back, so that one is left uncertain at the time whether an acute coronary thrombosis gave rise to the ectopic rhythm or whether the ectopic rhythm gave rise to an attack of coronary insufficiency. There are also patients in whom the circulation deteriorates as the rapid abnormal rhythm continues, and it is not long before shortness of breath, pulmonary râles and even pulmonary edema supervene. That is why I urge that the physician have a medication at his disposal for immediate use, especially in such cases, even if he remains in some doubt as to the exact nature of the ectopic rhythm, and it is for this purpose that I have recommended quinidine.

Let me come back for a moment to the matter of distinguishing the different forms of disordered rhythm. Both Dr. Pardee and Dr. Stewart indicated that it would be quite remarkable if a fellow could not distinguish clinically a paroxysm of auricular fibrillation from one of auricular tachycardia. I agree that in this case an error should be very infrequent but, on the other hand, how about the case of auricular flutter with a varying block? Can we be so sure about distinguishing this from auricular fibrillation by clinical means? There are also cases of premature contractions appearing in large numbers and at irregular intervals which are extremely difficult to distinguish from auricular fibrillation. I remember a striking experience many

years ago in the clinic of Dr. John Wyckoff. He was an expert in these matters. He then believed that the condition of frequent premature contractions was a precursor of auricular fibrillation. He showed us a patient with large numbers of premature contractions and predicted that one of these days we would find her in auricular fibrillation. Several years later he gathered a group of us at the clinic to listen to this patient and said that now she had auricular fibrillation as he had predicted she would have. Her heart beat certainly sounded like auricular fibrillation. An electrocardiogram was then taken which showed the same old condition, namely, extremely frequent auricular premature contractions. Since then I have encountered many similar problems in differential diagnosis. There is still another condition, namely, that of a paroxysm of auricular fibrillation with bundle branch block. In some the patient's normal rhythm shows a bundle branch block, and in others the bundle branch block develops as a result of the rapid rhythm of auricular fibrillation. I have rarely seen a case of this kind in which the error of calling it a ventricular tachycardia was not made. Such a tracing with a diagnosis of ventricular tachycardia was brought to my office from the Pediatric Department this very afternoon. There was no doubt of the error; it was a case of auricular fibrillation with a bundle branch block. Bundle branch block may complicate any of the supraventricular tachycardias and to distinguish these from ventricular tachycardia is a matter of first importance; for if it is a paroxysm of auricular tachycardia with bundle branch block, a large intravenous dose of a digitalis preparation may terminate the attack within a few moments. One would certainly not give digitalis to terminate a ventricular tachycardia because, first, it will fail to do so and, second, it might precipitate the disaster of ventricular fibrillation. Dr. Pardee spoke about an irregular rhythm in ventricular tachycardia as a condition much talked about but rarely seen in the electrocardiogram. That is also my experience. I have often wondered whether most of the cases presented as ventricular tachycardia with an irregular rhythm are not in fact cases of auricular fibrillation with a bundle branch block.

Dr. Deitrick's remarks on the necessity of considering the underlying cardiac state in patients with disordered rhythms are very well taken. An acute disorder of rhythm is a dramatic event and may engage our attention to the exclusion of more important problems in the particular case. I have seen doctors preoccupied with the paroxysm of auricular tachycardia and overlook the fact that it was caused by an acute coronary thrombosis, or with the repeated attacks of auricular fibrillation and overlook an underlying Graves' disease with predominant cardiac symptoms.

Dr. Smith referred to an experience in which quinidine used in a case of ventricular tachycardia caused cardiac standstill. I have seen a few of those. They are unpleasant experiences, to say the least. The patient may stop breathing, the eyes may roll up and within a few moments there is a convulsion. Dr. Deitrick, did this patient receive 0.6 Gm. of quinidine every two hours, and if so, how many doses?

DR. SMITH: The dose was 0.4 Gm.

DR. DEITRICK: And it was given every two hours.

DR. SMITH: The total dose was 2.4 Gm. over a period of ten hours.

DR. GOLD: This patient, therefore, received six doses of 0.4 Gm. each. Very well, let us analyze the situation. We have to assume that six doses of 0.4 Gm. each, or a total of 2.4 Gm., were required in this case to terminate the ventricular tachycardia. If five doses or 2 Gm. were sufficient, I assume you would not have given the sixth dose. It is clear that you had no choice since smaller doses than those which you used would have failed to abolish the ventricular tachycardia. There are animal experiments which show that a physiologic factor inherent in the sudden abolition of a rapid ectopic rhythm may cause cardiac standstill, for other pacemakers in the heart are

frequently suppressed during the period of a rapid ectopic rhythm. The duration of the arrest varies greatly from case to case; and if it lasts as long as ten or fifteen seconds, the patient may have an asphyxial convulsion. This phenomenon does not occur only when quinidine terminates an ectopic rhythm, for it is seen when carotid sinus pressure causes A-V block in auricular flutter or terminates a paroxysm of auricular tachycardia. Although it may be that quinidine contributes to the delay in the resumption of a rhythmic discharge, the hazard of cardiac standstill is always there in the abrupt termination of a rapid ectopic rhythm, regardless of the method by which this is accomplished. Is there any way of reducing this hazard? Yes, there is. When I use quinidine in an attack of ventricular tachycardia, I do not aim to abolish the abnormal rhythm by the direct action of the drug although it may take place before anything can be done about it. I aim to slow the tachycardia to a rate which may be permitted to continue for a protracted period without impairing the circulation, for example, from an initial rate of 200 per minute to 120 or 110 per minute. When the heart functions for some time at these slower rates, the other pacemakers recover and become ready to take over promptly when the ectopic rhythm is abolished, without the delay which may give rise to a convulsion when a very rapid rhythm is brought to an end abruptly. In treating patients with ventricular tachycardia in whom I have reduced the rate from 180 or so to about 120 and then examined the electrocardiogram, I have often thanked my stars that I had not given enough quinidine to abolish the abnormal rhythm, for the tracing showed a slow idioventricular rhythm without any P waves. Had the ectopic rhythm been abolished abruptly at that point, the heart would have been left without a pacemaker, and the patient would have experienced the same reaction you encountered in the case you described. After hours or a day or so, with this slower ectopic rhythm, a supraventricular pacemaker revives as shown by the appearance of P waves in the tracing and additional doses of quinidine may then be used safely to restore a normal rhythm in the event it does not take place spontaneously. My advice, therefore, in the treatment of ventricular tachycardia is to give 0.4 or 0.6 Gm. of quinidine every two or three hours, count the rate before each dose, continue this until the rate declines to about 120 or 110 per minute and then interrupt medication to see whether the normal rhythm will not reappear under these conditions. An electrocardiogram should be taken when the slower rates are present in order to determine whether auricular activity is in evidence and, if it is, additional doses should be given to restore normal rhythm, provided it is not already there. Large doses of quinidine act like atropine to speed up the sinus rate, and these rapid rates may lead one to assume that the ventricular tachycardia is still present unless a check is made with the electrocardiogram. There is much more to the expert management of an attack of ventricular tachycardia, but this plan avoids one of the major sources of risk.

DR. SMITH: Dr. Stewart, are there any comments you would like to make in relation to Dr. Gold's remarks? Perhaps you might wish to say something about the treatment of the patient with ventricular tachycardia who fails to respond to quinidine, and what to do for ventricular tachycardia that sometimes occurs as the result of digitalis poisoning.

DR. STEWART: Supraventricular tachycardia with bundle branch block has been reported in the literature. I do not know how many such cases there are, but they are so rare that the confusion of this condition with ventricular tachycardia is not likely to be a source of any considerable trouble.

In regard to the use of large doses of quinidine, one should bear in mind the danger of so poisoning the heart as to

suppress the sinus node. In such a case if the ventricular tachycardia is terminated the outcome may be fatal.

I might mention my experiences with cases of pericardiectomy for constrictive pericarditis which was performed by Dr. Heuer and Dr. Andrus. Frequent electrocardiograms were taken during the procedure and paroxysms of abnormal rhythm were often seen as the result of mechanical stimulation, but they ceased immediately when the surgeon gave the heart a rest.

Many of you will recall the patient here in New York Hospital who had a variety of abnormal rhythms. The attacks of nodal tachycardia were the most difficult to control in this case. In the several years of observation of this patient, during which she showed various abnormal rhythms, it sometimes seemed that digitalis was effective in preventing attacks over a long period of time and sometimes quinidine in maintenance doses seemed to prevent the paroxysms.

When a patient receives quinidine daily over long periods to prevent recurrences of paroxysms of tachycardia, an electrocardiogram should be taken from time to time to find out whether there is any widening of the QRS. This, I believe, is the only evidence of quinidine poisoning which one might be able to discover early.

Dr. Smith: I still should like to have an answer to my question on the treatment of ventricular tachycardia which fails to respond to quinidine, and the question on what to do for ventricular tachycardia which occurs in digitalis poisoning.

Dr. Stewart: Quinidine rarely fails to abolish ventricular tachycardia when the drug is used in adequate amounts. If it is urgent to stop the ventricular tachycardia, for instance, in the patient with a recent coronary occlusion, it is my practice to start quinidine at once without delaying to test for idiosyncrasy to the drug. I give 0.4 Gm. and repeat this every four hours. I do not give it at intervals of two hours. In most cases the abnormal rhythm is abolished with total doses up to 2.4 Gm. on the first day. If this proves insufficient, the dose may be increased by 0.4 Gm. the next day, and again by still another 0.4 Gm. on the third day. One should carefully watch for toxic effects.

In the group of patients who have been digitalized, mentioned by Dr. Smith, ventricular premature contractions may or may not be present; and then if quinidine is given, many ventricular premature contractions may be produced. There are reports in the literature to the effect that quinidine and digitalis together caused ventricular tachycardia, the beats arising alternately from the two ventricles. Most of these terminated fatally. There is really not much that one can do in such cases. If quinidine is continued, ventricular fibrillation may ensue and this is usually fatal. It is well to discontinue both drugs. Procaine may find a place in the treatment of this toxic effect.

Dr. Eggleston: May I make a remark on the paroxysms of auricular fibrillation which occur in thyrotoxic patients? I have not found anything which controls these paroxysms except therapy for the correction of the hyperthyroidism, namely, iodine, thiouracil and related compounds, or surgery. Neither quinidine nor digitalis is effective in preventing the paroxysms of auricular fibrillation until the hyperthyroidism has been brought under control.

Dr. Gold: I should also like to make a few supplementary remarks at this point. Dr. Stewart stated that bundle branch block so rarely complicates a supraventricular tachycardia or a paroxysm of auricular fibrillation as to present little or no problem in differentiating these from ventricular tachycardia. I encounter that problem not at all infrequently, and I wonder whether the view that it is a rarity does not arise from the very fact that the problem is not commonly considered and an erroneous diagnosis of ventricular tachycardia is made. As I have already mentioned, most of these cases which I have seen were erroneously labeled ventricular tachycardia.

A further word on the dosage of quinidine seems to me worth while. Suppression of the sinus node during the use of this drug in ventricular tachycardia or in the case of any other ectopic rhythm for that matter is not necessarily the result of improper dosage. One cannot say that in a particular case the ventricular tachycardia would necessarily have been abolished without the auricular standstill if smaller doses had been used, for in some of these cases, as the drug is continued, the electrocardiogram may reveal a marked slowing of the idioventricular rhythm from, let us say, 200 to 120 a minute; but even in the tracing showing the slow rate, the mechanism may still be that of ventricular tachycardia without P waves as evidence of auricular standstill. This simply means that in some cases of ventricular tachycardia the level of quinidine action necessary to abolish the idioventricular rhythm is sufficient to abolish the activity of the auricles; and that i smaller doses were given, the auricular activity would not be suppressed, but then also the ventricular tachycardia would not be abolished. It is simply a matter of good fortune that in the majority of cases sufficient differential in the sensitivity of the two structures to quinidine exists, so that it is possible to arrest the idioventricular pacemaker without inactivating the sinus node. The method I described for controlling ventricular tachycardia helps to insure against suppressing both auricular and ventricular activity at the same time by quinidine.

There is another point about quinidine dosage and the likelihood of successful control of an ectopic rhythm. A large proportion of the failures to abolish an abnormal rhythm by means of quinidine is due to inadequate dosage. If we pursue the plan of giving a dose of 0.4 or 0.6 Gm. at intervals of between two and four hours and continue that system until either the ectopic rhythm is brought under control or minor toxic effects appear, such as disturbing symptoms of cinchonism, vomiting or diarrhea, the number of failures will be greatly reduced. In the vast majority of cases which have come to my attention as failures, the drug was simply discontinued after a period of arbitrary dosage unrelated to either therapeutic or toxic effects.

Dr. Stewart referred to the widening of the QRS wave as evidence of quinidine toxicity and stressed the need of an electrocardiogram taken from time to time, which might show this effect, in patients who receive quinidine daily over long periods. I believe this is a useful device for avoiding more serious poisoning. We studied this phenomenon several years ago and found that daily doses of about 2 Gm. may prolong the QRS time by about 20 or 25 per cent. Some patients are much less sensitive and larger doses may be given before this effect occurs. It does not seem wise to increase the dose of quinidine beyond that which prolongs the QRS time by 25 per cent above the control for that person although it is possible that one can produce even greater QRS prolongation without serious consequences. In this connection perhaps we should call attention to the fact that if a patient receives a fixed daily dose for about five days and at the end does not show this effect, it is not necessary to take any more electrocardiograms later. This is so because quinidine cumulation, like that of many other drugs, is a self-limiting process, and all cumulation of quinidine that is going to take place with a fixed daily dose occurs during the first four or five days. Therefore, if a particular effect has not taken place by that time, there is little likelihood of its occurring later.

In relation to Dr. Smith's question as to how to treat ventricular tachycardia which is not controlled by quinidine even when the drug has been given to the point of toxic effects, the earlier comment by Dr. Pardee may be recalled. An intravenous dose of magnesium sulfate, 10 or 15 cc. of a 10 per cent solution, is sometimes quite effective. An intravenous dose of procaine might also be tried, but with this I have had no experience.

Dr. Smith has also asked about ventricular tachycardia due to digitalis poisoning. I would suggest that no attempt be made to terminate this by any drug. In experiments on animals, which were published several years ago, we found quinidine very effective in terminating the ventricular tachycardia induced by digitalis. It was usually a fleeting effect and seemed to be a result not only of direct action on the ventricle but also a result of the fact that the sinus node was so much accelerated as to make the auricular activity faster than the idioventricular activity. A source of serious danger appeared in these experiments, namely, the fact that ventricular arrest often occurred due to the fact that the dose of digitalis which had poisoned the heart sufficiently to induce ventricular tachycardia had also produced complete block by its direct action on the A-V node. Since the existence of such a block is masked in the electrocardiogram showing a ventricular tachycardia, it seems to me wiser to refrain from using quinidine or any other drug to abolish the ventricular tachycardia caused by digitalis poisoning. It is probably the lesser of the two evils to allow the ventricular tachycardia to continue until it disappears spontaneously as the elimination of the digitalis takes place.

Dr. N. T. Kwit: In regard to the dose of mecholyl I was surprised to hear that the range of doses for younger people was lower than that for older people. I would have expected the reverse since older people are so much more likely to have coronary disease which is sometimes stated to be a contraindication to the use of mecholyl. I recall an experience in which a man, fifty years of age, developed a paroxysm of auricular tachycardia for which I used mecholyl. He had never complained of angina of effort, but after a dose of 50 mg. subcutaneously and while the attack subsided, he developed a terrifying attack of substernal pain.

Dr. Walter Modell: It has been stated here that digitalis is effective in abolishing a paroxysm of auricular tachycardia and that the drug may also be continued to prevent recurrences. I believe I once heard Dr. Gold mention some tricks for increasing the efficacy of digitalis in a paroxysm of auricular tachycardia and auricular flutter.

Dr. Smith: What are they?

Dr. Gold: In a paroxysm of auricular tachycardia one is likely to use digitalis only after the various devices which have already been described have failed. The point I have in mind is based on the fact that digitalis increases the sensitivity of the heart to carotid sinus pressure. Inject 0.3 mg. ouabain intravenously and wait about thirty minutes. Now carotid sinus pressure may terminate the attack abruptly. If the dose of ouabain turns out to be too small for the particular patient, the tachycardia may return within a few minutes. In that event one may safely repeat the dose of ouabain and the carotid sinus pressure. This technic frequently makes it possible to abolish a paroxysm of auricular tachycardia with smaller amounts of digitalis. Any of the intravenous injectable digitalis preparations may be used for this purpose although the more rapidly acting ones are more practical.

There are several ways of applying digitalis in a case of auricular flutter. In many instances there is little more to it than the fact that a normal rhythm appears after very large doses of digitalis have been given. In others, however, the digitalis will convert the flutter into fibrillation, and the fibrillation may persist as long as the digitalis is continued. In these patients the restoration of a normal rhythm takes place only after the digitalis is discontinued. Here also a rapidly eliminated digitalis preparation is the most practical.

Dr. Smith: Dr. Pardee, could we have some remarks from you on the subject of heart block and the Adams-Stokes attacks?

Dr. Pardee: In patients subject to Adams-Stokes attacks, the diagnosis of the particular mechanism is very important. The mechanism is often one of prolonged A-V conduction in which there is a fleeting period of complete dissociation. This gives rise to spells of transient giddiness, usually

without convulsions, because the normal conduction soon reappears.

Among patients who have complete heart block and who develop more severe attacks of syncope there are two mechanisms. In one type the syncope is due to ventricular arrest. These patients usually have an irregular ventricular rhythm with a slow rate of 20 or so. In the second type the syncope may be associated with ventricular fibrillation. These patients may have a somewhat higher ventricular rate but the rhythm is apt to be interrupted by premature contractions. Such a finding between the attacks should make one suspect that the convulsive seizures are probably due to ventricular fibrillation. Digitalis and ephedrine to increase the rhythmicity of the myocardium are often helpful in the types of heart block in which the syncope is due to ventricular arrest, but they seem to aggravate the type in which ventricular fibrillation occurs. Sedatives, such as bromides or phenobarbital, seem to be helpful in the patients in whom convulsions occur as the result of ventricular fibrillation.

At this point it should be mentioned also that there is no contraindication to using digitalis in the patient with chronic heart block if heart failure is present.

DR. MODELL: How would you treat congestive failure which might develop during a paroxysm of one of the ectopic rhythms? Assume that you had not yet found the proper drug or combination of drugs to abolish the paroxysm. I should also like to know whether it is not true that the control of the failure sometimes abolishes the ectopic rhythm.

DR. SMITH: Dr. Deitrick, will you try your hand at this?

DR. DEITRICK: If it happens to be a supraventricular tachycardia, it is fortunate because one can then use digitalis freely. In the case of ventricular tachycardia I do not have the courage to digitalize even in the presence of congestive failure. I try to stop the paroxysm of tachycardia as quickly as possible.

DR. MODELL: How about using a mercurial diuretic?

DR. DEITRICK: I would use it but I do not think that is the answer to the problem. One simply has to abolish the ectopic rhythm before the function of the heart can be improved materially.

DR. PARDEE: I know of two patients with ventricular tachycardia in whom failure developed and who were treated with digitalis. Both of them died.

DR. SMITH: Was quinidine used in these cases?

DR. PARDEE: Quinidine had been used but was ineffectual. Everything we tried failed.

DR. SMITH: I take it that the last thing you tried was digitalis.

DR. PARDEE: Yes. The ventricular tachycardia was somewhat slowed by quinidine but it was not possible to abolish the rhythm. When the patient developed frank signs of failure, he was digitalized.

DR. GOLD: I think Dr. Modell's question merits more attention. An intensive course of dehydration by the use of milk as the sole diet, liberal water intake and a daily intramuscular injection of 2 cc. of a mercurial diuretic should go a long way in helping to control the congestive failure which develops during a paroxysm of a rapid ectopic rhythm. I am inclined to believe that these measures are more effective than digitalis in such cases, so that one does not need to worry too much over the fact that digitalis is omitted.

There is an important point in his second question also. Paroxysms of ectopic rhythm are sometimes the first manifestations of a failing heart. There may be paroxysms of auricular fibrillation, auricular tachycardia, ventricular tachycardia and others. An effective course of dehydration by means of salt restriction and frequent doses of the mercurial diuretic sufficient to reduce the patient to his "dry weight" is often successful in abolishing attacks of ectopic rhythm and preventing their recurrence.

DR. MODELL: I was interested in the comment on the matter of having atropine

on hand in the event that carotid sinus pressure caused cardiac asystole. It is not quite clear to me what purpose it would serve since if there is asystole there is no circulation, and even if the atropine were injected into the vein or directly into a chamber of the heart, there would be no means of transport to the site of its action. I know that carotid pressure may produce cardiac standstill of duration that is very disquieting; it may last long enough to give rise to an asphyxial convulsion, but I believe it is a fact that escape from vagal control is the rule and that disaster from the use of carotid pressure is extraordinarily rare if indeed it occurs at all.

VISITOR: I would like to ask Dr. Gold what he does for a paroxysm of sinus tachycardia.

DR. GOLD: This is the most common form of tachycardia and we have no specific treatment for it.

DR. SMITH: How about removing the cause?

DR. GOLD: That is what we try to do but we cannot boast of our success. I assume that we may omit from consideration the patient with Graves' disease or with fever in whom sinus tachycardia occurs. The patients who complain of attacks of rapid heart action and in whom these turn out to be paroxysms of sinus tachycardia are individuals with autonomic imbalance, disturbed psychic states, tension states and the instability of the menopause. We have no drugs which act directly to produce persistent slowing of the sinus rhythm. We try to treat the nervous state. We sometimes use sedatives or suggestion or whatever else seems indicated by the various and sundry problems presented by the particular individual. They may improve but, on the whole, the therapeutic results are not particularly striking.

DR. SMITH: Are there any further questions?

VISITOR: Suppose you were faced with the problem of a patient who had just suffered a myocardial infarction which precipitated auricular fibrillation with a ventricular rate of 160 a minute. What would you do? Would you try to abolish the fibrillation or merely try to slow the ventricular rate?

DR. SMITH: Would you answer that, Dr. Eggleston?

DR. EGGLESTON: I have been confronted with that problem on several occasions. I do not try to restore the normal rhythm. Very often the auricular fibrillation which occurs in association with an acute coronary thrombosis is of short duration. It has been my practice to resort to digitalis to slow the ventricular rate and to relieve or prevent congestive failure. I do not believe there is any contraindication to the use of digitalis even in fresh infarction.

SUMMARY

DR. GOLD: The treatment of disorders of cardiac rhythm was explored in this conference. This was a very large undertaking. There are several types of disorders of rhythm; there are various devices for distinguishing one from another. It is important to do so for there are significant differences in the treatment of each, and the most successful results depend on the use of measures specifically suited to the particular problem. A special conference could be profitably devoted to any one disorder of rhythm.

There has been no attempt to exhaust the subject, but many points of practical interest have been brought out in the account of experience and opinion by the various participants. Many of the details cannot be satisfactorily summarized without repeating the conference. The following disorders of rhythm received attention: premature contractions, auricular and nodal tachycardia, auricular flutter, auricular fibrillation, ventricular tachycardia and heart block. There was some discussion of the management of congestive failure in the course of a paroxysm of abnormal rhythm and the problem of ectopic rhythms occurring in the hyperthyroid state. It was pointed out that three distinct problems prevail in cases of disordered rhythm, namely, those in whom the disordered rhythm is a chronic phenomenon

and is to be allowed to continue, those in whom an acute paroxysm needs to be terminated and those in whom the problem is essentially one of preventing recurrences. Means for differential diagnosis were described, namely, certain clinical features, the electrocardiogram, carotid sinus pressure and various devices exerting similar effects.

The application of several drugs was discussed in some detail, such as quinidine, digitalis, magnesium sulfate, procaine, mecholyl, ipecac, ephedrine, morphine and other sedatives. In a patient with a paroxysm of rapid heart action which does not appear to be damaging the circulation unduly, there are some who prefer to give a dose of morphine to make the patient more comfortable and let the problem rest until the abnormal rhythm ceases spontaneously. Digitalis appears to be the drug of choice for the paroxysm of auricular and nodal tachycardia. While mecholyl is very effective, it is so apt to produce disturbing symptoms that it is best to keep it in reserve for use when other measures fail. Quinidine is the standard remedy for an attack of ventricular tachycardia; and when for one reason or another it proves inadequate, an intravenous injection of magnesium sulfate is sometimes effective. There are risks involved in the use of all these drugs to abolish a paroxysm of abnormal rhythm, and technics were described for reducing the hazards to a minimum.

Attention was called to the fact that there are many situations in which a differential diagnosis among the disorders of rhythm is difficult or impossible to make, but that even under those conditions, a specific form of therapy is still available; for quinidine is highly effective against five of the more common disorders of rhythm: premature contractions, paroxysmal auricular tachycardia, auricular flutter, auricular fibrillation and ventricular tachycardia. Strong emphasis was placed, however, on the desirability for making every effort to establish the precise mechanism before treatment is started, for only then is the most rational and effective plan of therapy possible.

Finally, the point was made that one should always bear in mind the underlying state of the heart in which a rapid ectopic rhythm has suddenly appeared. The abnormal rhythm is a dramatic event and may engage the attention of the examiner to the exclusion of other factors of far greater importance than the abnormal rhythm, such as Graves' disease or an acute coronary thrombosis.

Clinico-pathologic Conference

Progressive Congestive Heart Failure with Peripheral Vascular Collapse*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. I., (B. H. History No. 140,836), a forty-six year old married negress, entered the Barnes Hospital for the first time on November 4, 1946, complaining of shortness of breath and swelling of the abdomen and legs. The family history was of interest in that the patient's mother died late in life from "leakage of the heart." The patient was one of nineteen children, eight of whom were living. No details were known regarding the causes of death of the other siblings.

Prior to the age of twenty-two the patient had recurrent attacks of chills and fever which had been diagnosed as malaria but subsequently she had very few such episodes. She did not recall ever having scarlet fever or rheumatic fever but stated that she had always been subject to "head colds," and for the ten years prior to admission she had occasional paroxysms of wheezing which lasted two to three hours; these occurred particularly in damp weather. The patient had no other symptoms suggestive of allergic disease. Throughout most of her adult years she had recurrent nose bleeds. When she was eighteen she was told that the epistaxes were due to high blood pressure and a similar comment was made to her by a physician four years before entry into the hospital. Over a period of some thirty years the patient had severe headaches every few months which lasted three to four days.

Four years before admission she was told that she had "bad blood," and was given a total of ten intramuscular injections at weekly intervals. She denied any local lesion or eruption in earlier life suggestive of syphilis. She had one child; two other pregnancies terminated spontaneously at four months. For many years she had weighed between 220 and 230 pounds. Until the age of thirty she had worked as a cotton picker but subsequently her activities were those of a housewife. Her habits were not remarkable.

Three years before admission the patient for the first time noted swelling of the ankles which was more pronounced in the evening and which disappeared overnight. She was free of other signs and symptoms until one year later when her abdomen became distended; soon after she noted shortness of breath on moderate exertion. She consulted a physician who prescribed "one green pill daily." She took the pills for two weeks after which the ankle swelling disappeared and did not recur for several months. When the swelling again became apparent, she resumed taking the green pills and once again noted improvement. The program of self-medication was continued for about one year but during this period the patient's abdomen gradually became larger.

One year before admission she consulted another physician who gave her an injection, subsequent to which she passed a large amount of urine and the swelling in her abdomen quickly subsided. When her abdomen again became distended after several months, she consulted the physician

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who repeated the injection and once more an apparently satisfactory diuresis resulted. Four months before entry she was seen at another hospital at which a paracentesis was performed. She was told to follow a salt-poor diet and was given medication, the nature of which was not known. Her symptoms improved a great deal following institution of this regimen and she continued to do well until a neighbor advised her that a teaspoonful of salt a day would be very beneficial. The patient followed this suggestion and became markedly edematous once more. Dyspnea on exertion became extreme and she was particularly short of breath at night. She stated that for several years prior to entry she had occasional short fleeting pains over her chest which came on with exertion and were relieved by rest. No further details in regard to this complaint could be elicited, however, and the patient's only additional complaint was that she occasionally suffered palpitation which would "shake my whole body."

Physical examination at the time of admission revealed the patient's temperature to be 36.8°c., pulse 100, respirations 32 and blood pressure 130/85. The patient was an obese negress who was acutely ill and obviously uncomfortable. Dyspnea was so marked that she had great difficulty in speaking. The respirations were shallow but cyanosis was not present. The pupils were round, regular and equal and reacted to light and accommodation. The sclerae were not icteric. Examination of the fundi revealed no hemorrhages or exudates but the arterioles were markedly tortuous. No abnormal findings were noted in the upper respiratory tract. The trachea was in the midline. The neck veins were markedly engorged. The upper anterior chest was prominent and heaving pulsations could be seen over that area. The lungs were resonant to percussion throughout and breath sounds were well heard. An occasional râle was present at the lung bases. The cardiac impulse was heaving over the entire precordium. No thrills were palpated. The left border of cardiac dullness was 14 cm. from the mid-sternal line in the fifth interspace and right border dullness was 8 cm. from the sternum in the fourth interspace. The sounds were loud; a gallop rhythm was audible at the apex and occasional extrasystoles were heard. The first sound was normal in intensity; it was followed by a grade III systolic murmur which was well transmitted to the axilla and was heard also to the right of the sternum. No diastolic murmurs were described and P_2 was not accentuated. The abdomen was enormously distended and the signs of ascites were striking. Adequate palpation was not possible because of the huge amount of peritoneal fluid. Pelvic and rectal examination were both normal. There was 4 plus pitting edema extending above the knees and marked sacral edema was likewise present. The neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 4,160,000; hemoglobin, 12 Gm.; white cells, 7,200; differential count: eosinophiles, 2 per cent; juvenile forms, 2 per cent; stab forms, 2 per cent; segmented forms, 65 per cent; lymphocytes, 25 per cent; monocytes, 4 per cent. Urinalysis: albumin, trace; sediment, occasional granular cast. Blood Kahn test: positive (20 units). Stool examination: guaiac negative. Blood chemistry: nonprotein nitrogen, 15 mg. per cent; total protein, 4.2 Gm. per cent; albumin, 2.5 Gm. per cent; globulin, 1.7 Gm. per cent; icterus index, 18 units; cephalin-cholesterol flocculation test, negative; alkaline phosphatase, 3 Bodansky units. Venous pressure: 330 mm. of saline. Circulation time (decholin): 75 seconds. Roentgenogram of the chest: "There is marked enlargement of the cardiac shadow both to the right and left. The aorta is lengthened. The lungs appear clear." Electrocardiogram: P-R interval, .24 seconds; T waves, low upright in lead I; premature ventricular contractions.

Soon after admission an abdominal paracentesis was performed and 10 liters of slightly turbid, straw-colored fluid were removed. On examination the specific

gravity of the fluid was 1.015 and it contained 195 mononuclear cells. Following paracentesis, re-examination of the abdomen revealed the liver edge to be 10 cm. below the right costal margin and pulsation of the liver was described. Fluoroscopic examination of the chest revealed the heart to be globular in shape with enlargement of both the left and right sides. The aortic shadow was small. The pulmonary conus did not seem to be enlarged.

The patient was given 1.2 mg. of digitoxin orally and on the following day the gallop rhythm disappeared. Then for the first time a long, loud, mid-diastolic rumble was heard at the apex; the systolic murmur previously described was still present. The diastolic murmur persisted thereafter. The patient was given ammonium chloride and mercupurin and her improvement was striking. During the first week of her hospital stay she lost 53 pounds. The liver became smaller in size and no longer pulsated. The venous pressure fell to 78 mm. of saline and the decholin circulation time decreased to 28 seconds. The cardiac rhythm which had been regular became grossly irregular and a subsequent electrocardiogram showed auricular fibrillation. Because of the positive serologic test for syphilis, a lumbar puncture was performed; the spinal fluid was entirely normal. The patient left the hospital on November 16, 1946, to be followed in the medical clinic. She was advised to follow a salt-free diet and to continue taking digitoxin.

She did quite well for about one month but then ankle edema, abdominal swelling and dyspnea began to reappear. Although she had apparently adhered to the therapeutic regimen quite closely and was faithful in her clinic attendance, her condition became progressively worse and on February 23, 1947, she was re-admitted to the Barnes Hospital. In the week before admission she had developed a loose, productive cough.

Physical examination at the time of entry revealed the temperature to be 37.2°C., pulse 90, respirations 26 and blood pressure 170/80. The following changes from those previously recorded were described: The patient was slightly dyspneic and orthopneic. Her sclerae were moderately icteric and the eyeground vessels showed tortuosity and narrowing. There was marked distention of the neck veins and of the veins of the forehead. Examination of the lungs revealed fine, moist râles at both bases. The left border dullness was noted 11 cm. from the mid-sternal line in the fifth interspace. The rhythm was totally irregular with long periods of coupling. A harsh, grade IV, high-pitched, systolic murmur was heard in the mitral area and a similar murmur could be heard over the tricuspid area. The mid-diastolic apical rumble was audible but seemed distant. The abdomen was distended with evidence of a moderate amount of fluid. A midline diasthesis of the rectus muscles permitted a 4 by 4 cm. herniation of the abdominal contents. The hernia was tender to palpation and painful even when not touched. The liver was felt 16 cm. below the costal margin in the midline. It was markedly tender and systolic pulsations were easily felt. Four plus brawny pitting edema in both lower extremities extended up to the sacrum.

The laboratory findings were as follows: Blood count: normal throughout. Urinalysis: albumin, 3 plus; sediment, occasional granular cast. Blood Kahn test: positive (4 units). Blood chemistry: non-protein nitrogen, 17 mg. per cent; total protein, 7.7 Gm. per cent; albumin, 4.0 Gm. per cent; globulin, 3.7 Gm. per cent; icterus index, 18 units; cephalin-cholesterol flocculation test, 2 plus; CO_2 combining power, 47.7 volumes per cent; chloride, 100 mEq./L.; bromsulfalein dye retention, 40 per cent in 30 minutes. Venous pressure: 350 mm. of saline. Circulation time (decholin): 28 seconds. Roentgenograms of the chest: "The findings are not unlike those previously noted except that the left border of the heart is not as sharply outlined and there appears to be a diffuse homogeneous shadow obliterating the left costophrenic angle which does not have the appearance

of fluid. A flat film of the abdomen shows a calcified mass approximately 5.7 cm. in diameter in the left side of the pelvis, presumably a calcified myoma." Electrocardiogram: Auricular fibrillation; abnormal form of ventricular complex; full intraventricular conduction time and left axis deviation. Phonocardiogram was interpreted as showing no evidence of the murmur of tricuspid stenosis although there was some suggestion of a tricuspid systolic murmur. Special studies of the liver pulsations suggested that they were due to the marked impact of the heart in systole.

On admission the patient was fluoroscoped and the trachea was found to be pushed slightly to the right. The heart was greatly enlarged to both right and left, the left ventricle being particularly huge. The pulmonary conus was quite prominent. A barium swallow revealed deviation of the esophagus backward and to the right in the region of the cardiac base.

The patient's pain at the site of the abdominal hernia became more severe. She was given morphine; the hernia was then reduced easily by manipulation. Therapeutic measures were instituted which included a salt-free diet and 0.2 mg. of digitoxin and 12 Gm. of ammonium chloride daily. Mercupurin was given intravenously at frequent intervals. Once again the patient responded well and by the fourth day had lost 21 pounds. The râles in her chest disappeared and she was more comfortable. She was allowed to be up and about and aside from complaining of cramps in the right calf muscle she was free of symptoms. Examination of both legs showed no abnormalities. On the morning of the tenth hospital day the patient complained of nausea and weakness and she began to perspire. When questioned by a house officer, she also complained of substernal pain. Examination of the heart revealed the findings to be unchanged. Her blood pressure at the time was 180/120. That afternoon the patient developed severe lower abdominal pain and definite tenderness was noted on palpation over that area. The skin was cold and perspiration was profuse. The patient vomited approximately 1 liter of undigested material and her blood pressure gradually fell to 110/82. The heart sounds became poorer in quality and a protodiastolic gallop rhythm became audible. The abdominal tenderness increased progressively and an electrocardiogram was suggestive but not conclusive of myocardial infarction. Two hundred fifty cc. of pooled plasma were given slowly but the patient failed to improve. She continued to perspire profusely, became unresponsive, stuporous and finally comatose and expired within a few hours of the onset of abdominal pain. During the last twenty-four hours in the hospital her temperature, which had been at levels just above normal, rose to 39.6°C. Death occurred on March 5, 1947.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: I believe we are faced with two major questions: the first in regard to the type of heart disease with which the patient was afflicted and the second, the cause and nature of the terminal episode. Dr. Massie, will you open the discussion by telling us what type of heart disease you believe this patient had?

DR. EDWARD MASSIE: Chiefly on the basis of the auscultatory findings, it seems quite likely that the patient had rheumatic heart disease. She had the classical murmurs of mitral stenosis and insufficiency and even in the absence of a typical history I believe the diagnosis is still obvious. It is well worth pointing out that she had numerous nose bleeds in earlier life which is at least consistent with rheumatic infection.

DR. ALEXANDER: She was told at the age of eighteen that she had hypertension and that the elevated blood pressure was the cause of her epistaxes.

DR. MASSIE: I think that explanation is quite unlikely. It would be unusual for a patient to have epistaxes on the basis of hypertension at the age of eighteen and live to the age of forty-seven.

DR. ALEXANDER: Is death at the age of forty-seven in keeping with the course of rheumatic heart disease?

DR. MASSIE: Yes, it certainly is.

DR. ALEXANDER: Does the description of the heart size and the contour seem consistent with the diagnosis of rheumatic heart disease?

DR. MASSIE: Yes, I think the findings are quite consistent with rheumatic valvular deformities, more so really than with hypertension or coronary artery disease.

DR. ALEXANDER: Why should the left ventricle have become so large?

DR. MASSIE: I believe the description states that the heart was enlarged both to the left and the right and that the right-sided enlargement was quite striking. I am impressed by the latter fact for I believe it favors the diagnosis of rheumatic heart disease. In hypertension left ventricular enlargement is common but the right side does not increase to such a degree.

DR. ALEXANDER: Dr. Bottom, do you care to comment?

DR. DONALD S. BOTTOM: I think that globular contour of the heart as seen in the x-ray films was quite in keeping with the diagnosis of mitral valvular disease.

DR. ALEXANDER: In other words, the evidence both from physical examination and from x-ray examination certainly favors the diagnosis of rheumatic heart disease. Furthermore, the patient was given a barium swallow and the esophagus was noted to be deviated. What interpretation is given to that finding, Dr. Glaser?

DR. ROBERT J. GLASER: It is indicative of left auricular enlargement resulting from mitral stenosis.

DR. ALEXANDER: Dr. Smith, would you care to defend the diagnosis of hypertensive cardiovascular disease?

DR. JOHN R. SMITH: No, I would not. In the first place, the patient's blood pressure was not significantly elevated. Secondly, as Dr. Massie has stated, the rather typical murmurs and the heart size are more in keeping with rheumatic heart disease than with hypertensive cardiovascular disease.

DR. ALEXANDER: She had been told twice in her life, once at the age of eighteen and again approximately at the age of forty-three, that she had hypertension. The eyeground changes were somewhat suggestive of hypertension, particularly on her second admission, and the radiologist told us that she had a lengthened aorta. Terminally, the electrocardiogram suggested coronary abnormalities. What importance do you attach to these data?

DR. SMITH: I believe these vascular changes were probably due to arteriosclerosis and I am unable to support the diagnosis of hypertensive cardiovascular disease.

DR. ALEXANDER: Dr. Scott, do you think the patient possibly had syphilitic heart disease?

DR. VIRGIL C. SCOTT: No, I see no evidence for that diagnosis.

DR. HENRY A. SCHROEDER: I believe it is likely that this patient had hypertensive cardiovascular disease. Aside from the murmurs all the findings are consistent. She had a history of hypertension and lack of elevation of the blood pressure is not uncommon in the presence of cardiac insufficiency.

DR. ALEXANDER: Her blood pressure was recorded twice daily during her first admission and all the values were well within normal limits. On the second admission the first value recorded was 170/80. Other readings, in general, were within normal limits.

DR. SCHROEDER: I still do not believe that the level of blood pressure in the presence of cardiac failure is significant one way or another in regard to the presence or absence of hypertensive cardiovascular disease. Furthermore, the description of the retinal vessels, particularly on the second admission, is consistent with hypertension. In regard to the x-ray findings it seems likely to me that the contour was distorted by cardiac dilatation and probably by enlargement of the auricles which one would expect in right-sided heart failure. I think murmurs such as were described

here may occasionally be seen in the presence of cardiac insufficiency and although they favor rheumatic heart disease I do not think that they definitely substantiate that diagnosis.

A STUDENT: Is auricular fibrillation more compatible with one diagnosis than the other?

DR. ALEXANDER: Auricular fibrillation may occur with either of the types of heart disease we are discussing.

DR. MASSIE: Auricular fibrillation makes it more difficult to hear mitral diastolic murmurs. In view of the fact that the combination of hypertensive and rheumatic heart disease is not uncommon I believe it is possible that the patient had both. If she had both, all the findings could easily be explained.

DR. ALEXANDER: Dr. Smith, do you believe the patient had a tricuspid lesion?

DR. SMITH: She certainly may have had. Very large hearts may be produced by tricuspid lesions, particularly tricuspid insufficiency.

DR. ALEXANDER: That lesion, of course, would be due to rheumatic heart disease, would it not?

DR. SMITH: Yes.

DR. SCHROEDER: In the presence of marked cardiac dilatation, functional tricuspid insufficiency may develop which may be indistinguishable from that of an actual abnormality of the tricuspid valve itself.

DR. ALEXANDER: Do you believe that in this case cardiac insufficiency, on the basis of hypertensive and arteriosclerotic coronary artery disease, was of sufficient degree that the tricuspid valve was functionally involved?

DR. SCHROEDER: I have seen cases of predominantly right-sided failure in which the patient developed a high venous pressure and a pulsating liver; at autopsy no tricuspid abnormality was apparent.

DR. SMITH: In passing we should mention that chronic pericarditis may give rise to a clinical picture much like the one with which we are faced here, that is, a markedly enlarged heart with signs of right-sided failure, high venous pressure, chronic passive congestion and cardiac cirrhosis.

DR. MASSIE: One point definitely against the diagnosis of pericarditis here is the fact that the patient's venous pressure fell to within normal limits; in pericarditis, either constrictive or adhesive, that is not usually the case for even when such patients improve their venous pressure remains at a high level.

DR. SMITH: I agree that the diagnosis of pericarditis is difficult to support when the venous pressure is not elevated but occasionally, even in the presence of pericarditis, it is not particularly high.

DR. ALEXANDER: When we speak of pericarditis we should think of two types. There may be actual constriction of the pericardium at the point where the great veins enter the heart. On the other hand, there may be chronic pericarditis consisting of mediastinal adhesions or of adhesions between the myocardium and pericardium itself with obliteration of the pericardial space. Now, if the great veins are constricted, I do not see how the venous pressure could fall, even with improvement, to the degree which was seen in this patient.

DR. MASSIE: I agree that the drop in venous pressure of the magnitude recorded here would be very surprising in pericarditis. I should like to mention further that the greatest degree of tricuspid insufficiency occurs in association with mitral stenosis because of the right ventricular enlargement and dilatation which leads to dilatation of the tricuspid valve ring.

A STUDENT: Is it possible that the patient had an interventricular septal defect with a paradoxical embolus arising in the leg vein and going to one of the mesenteric arteries?

DR. ALEXANDER: That is a very interesting suggestion which would perhaps explain the calf pain and the final abdominal episode. Dr. Massie, would you care to comment on this point?

DR. MASSIE: I think the systolic murmur is better explained on the basis of mitral insufficiency than by a septal defect and,

therefore, the only reason for bringing in that suggestion is, of course, to base the cause of death on a paradoxical embolus.

DR. GLASER: One other diagnostic possibility which should be mentioned in passing is Lutembacher's syndrome, patent foramen ovale with mitral stenosis. I believe the patient had rheumatic heart disease and not Lutembacher's syndrome, however.

DR. ALEXANDER: That is an interesting suggestion which certainly should be mentioned. I believe it is interesting that this patient had marked edema and ascites for a long period of time before she developed shortness of breath. Dr. Moore, would you care to comment?

DR. CARL V. MOORE: I think she simply had right-sided failure for several years and it was not until she developed left-sided failure that the shortness of breath, dyspnea and cough became apparent.

DR. ALEXANDER: What abnormalities would you expect to find in her liver?

DR. C. V. MOORE: I should expect to find the changes of so-called cardiac cirrhosis.

DR. ALEXANDER: Dr. Wade, do you think she had Laennec's cirrhosis?

DR. WADE: I do not see much evidence to support that diagnosis.

DR. ALEXANDER: Do you believe then that she will have cardiac cirrhosis as Dr. Moore suggests?

DR. WADE: Yes, I would think it quite likely.

DR. HAROLD A. BULGER: When in a negro patient murmurs suggestive of rheumatic heart disease are noted, the diagnosis of sickle cell anemia should always be considered.

DR. ALEXANDER: Dr. Moore, do you believe that the cardiac manifestations here may have been due to sickle cell anemia?

DR. C. V. MOORE: I believe that Dr. Bulger's suggestion is a very good one indeed, but I do not believe it holds here because the patient's blood count was repeatedly normal. If this had been sickle cell anemia, there should have been an anemia at one time or another.

DR. ALEXANDER: Dr. Scheff, prior to the terminal episodes the patient apparently suffered great pain from an abdominal hernia which was reduced after she had been given suitable sedation. Some days later she developed signs of peripheral vascular collapse following severe lower abdominal pain. Do you think that she probably had an intestinal lesion?

DR. HAROLD SCHEFF: I think one must certainly consider an occlusion of one of the mesentery vessels, either a mesentery thrombosis or an arterial embolus.

DR. ALEXANDER: Is not an embolus to the mesenteric arteries very rare?

DR. SCHEFF: Yes, it is rare but I believe it is more frequent than mesenteric thrombosis.

DR. SCHROEDER: This patient lost 21 pounds in four days and apparently was given considerable mercurial diuretics intravenously. She complained of cramps in her calf, had nausea, weakness, perspired profusely and also noted abdominal and substernal pain. In this connection we should mention a syndrome known as hypochloremic azotemia which may cause renal shutdown and is often associated with the use of mercurial diuretics. It is probably due to loss of chloride and can be reversed by administration of salt.

DR. ALEXANDER: Would that diagnosis be substantiated at the time of autopsy?

DR. SCHROEDER: I do not think so.

DR. ALEXANDER: I believe it is a very good point. Dr. Massie, do you believe the terminal event may have been coronary occlusion? The electrocardiographic changes were said to have suggested that possibility.

DR. MASSIE: I reviewed the electrocardiograms in this case and do not think that the changes really suggested myocardial infarction. I doubt that the patient had an infarct.

DR. ALEXANDER: In summary, it appears that the cardiologists, in general, favor rheumatic heart disease with mitral and possible tricuspid involvement as the most likely diagnosis. It is also thought that the

patient will have cardiac cirrhosis; pericarditis has been mentioned in passing and a vascular accident involving one of the abdominal mesenteric vessels has been proposed as a possible cause of abdominal pain.

Clinical Diagnosis: Rheumatic heart disease with mitral insufficiency; mitral stenosis; ? tricuspid insufficiency, marked cardiac insufficiency, advanced; cardiac cirrhosis; ? mesenteric or embolic thrombosis.

PATHOLOGIC DISCUSSION

DR. PARKER R. BEAMER: External examination of the body revealed moderate pitting edema of the legs but there were no other significant findings. When the chest was opened, no fluid was present in either pleural cavity. The pericardial sac contained 15 cc. of clear yellow fluid. The heart was markedly enlarged, weighing 810 Gm. In the region of the left atrioventricular groove an irregular area of the epicardium measuring 15 by 5 cm. was covered by a thin layer of gray, friable, loosely adherent material. Elsewhere the epicardium was thickened and opaque. The wall of the right ventricle measured 6 mm. in thickness and the wall of the left ventricle 16 mm. in thickness. Throughout the myocardium there were indistinct linear foci of gray-white fibrous tissue. The endocardium lining the chambers of the heart was not unusual except for slight increase in thickness and opacity in the left atrium above the mitral ring. Similar thickening of slight degree involved the free edges of the tricuspid and mitral valves but the chordae tendineae were not unusual. Between the cusps of the pulmonary and aortic valves there were a few delicate adhesions. The ostia of the coronary arteries were widely patent and dissection revealed no significant abnormalities in the branches of either vessel. The wall of the aorta was slightly thickened and several irregular, firm, slightly raised yellow plaques were apparent on the intimal surface. Just above the aortic valve there were a few indistinct and poorly outlined continuous areas of wrinkling of the intimal surface over firm, pearl-gray foci of thickened intima. In the subjacent media a few minute red spots were apparent.

The visceral and parietal pleural surfaces were smooth and glistening. All lobes of the lungs were slightly to moderately subcrepitant. The cut surfaces were dark red and frothy sanguineous fluid could easily be expressed. The mucous membranes of the bronchi were red and swollen. A calcified nodule 1 cm. in diameter was present in the peripheral portion of the lower lobe in the left lung and a similar focus 7 mm. in diameter was found in a tracheobronchial lymph node on the left.

The liver was slightly enlarged, weighing 1,820 Gm; its capsule was smooth and glistening. The substance cut with increased resistance and the surface was firm, mottled and slightly nodular. In some areas the architectural pattern was distinct, revealing well outlined lobules with dark red-brown central areas some of which, in turn, were partially circumscribed by indefinite yellow-brown foci. The portal areas were apparent in many instances as irregular gray-white linear foci. Scattered throughout the parenchyma, pale brown nodules up to 1 cm. in diameter were seen. These protruded slightly above the surface of the adjoining hepatic lobules.

The kidneys each weighed 180 Gm. The capsules stripped easily, revealing finely granular surfaces. In each kidney a relatively deep stellate scar, 7 by 3 mm., extended into the cortex for a short distance. In one or two areas in each kidney there were indistinct, broad, flat-based scars which involved only the superficial portions of the cortex. The dark red blood pyramids of both kidneys contrasted sharply with the pale red-brown cortical regions.

Examination of the abdominal contents was not remarkable. There was no evidence of vascular occlusion.

It can be seen that the principal disease which gave rise to the signs and symptoms presented by this patient was one which produced dilatation of the heart and, subsequently, hypertrophy to an advanced degree.

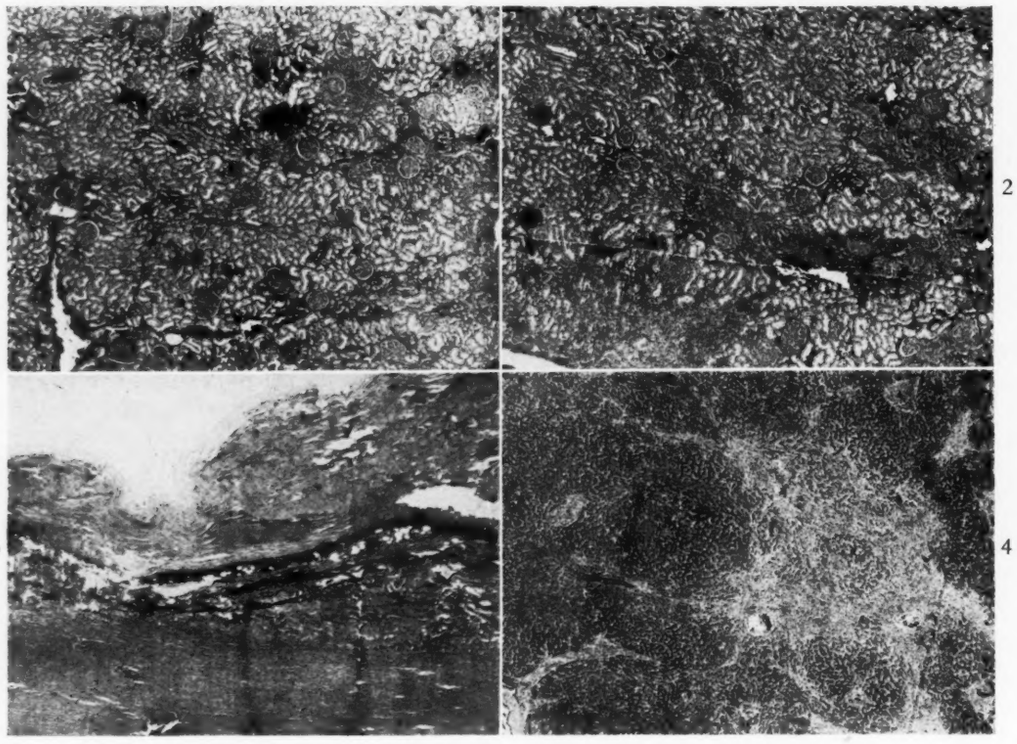

FIG. 1. Section of one kidney showing a slight degree of chronic pyelonephritis.
FIG. 2. A section of the other kidney with changes similar to those in Figure 1.
FIG. 3. Low power view of the wall of the aorta showing changes in the intima due to arteriosclerosis and changes in the media and adventitia which are those of syphilitic aortitis.
FIG. 4. Section of the liver showing an area of fibrosis. The general picture is that of long-standing chronic passive congestion leading to congestive cirrhosis.

Categorically, there are four common types of heart disease which result in dilatation and hypertrophy: these include rheumatic heart disease, syphilitic heart disease, hypertensive cardiovascular disease and congenital anomalies. In this case congenital anomaly may be eliminated on the basis of gross examination. If the enlarged heart were the result of rheumatic or syphilitic disease, one would ordinarily expect to find profound damage in the cardiac valves rather than the relatively minor changes noted in this instance. Likewise, the extent of the anatomic lesions noted grossly in the kidneys and vascular system hardly seems adequate to explain the amount of hypertrophy observed in the heart. Therefore, in order to reach satisfactory conclusions regarding the nature of the disease, we must turn to the microscopic sections and attempt to integrate them with the clinical findings and gross observations.

Figures 1 and 2 illustrate changes which are representative of those seen in both kidneys. There is slight to moderate thickening of the walls and narrowing of the lumina of small and medium-sized arteries in the renal substance. In an area not illustrated here a deep scar extended from the cortex to the corticomedullary junction; the glomeruli within the involved region were obliterated and there was loss of tubular structure. These changes are characteristic of arterial scars but have little if any clinical significance. In the sections shown there are a few irregular and poorly defined foci of lymphocytes and larger mononuclear cells within the interstitial tissue. However, this change, which represents a slight degree of pyelonephritis, is so limited that it may be readily concluded that the pathologic changes within the kidney are not adequate to account for the tremendous hypertrophy of the heart.

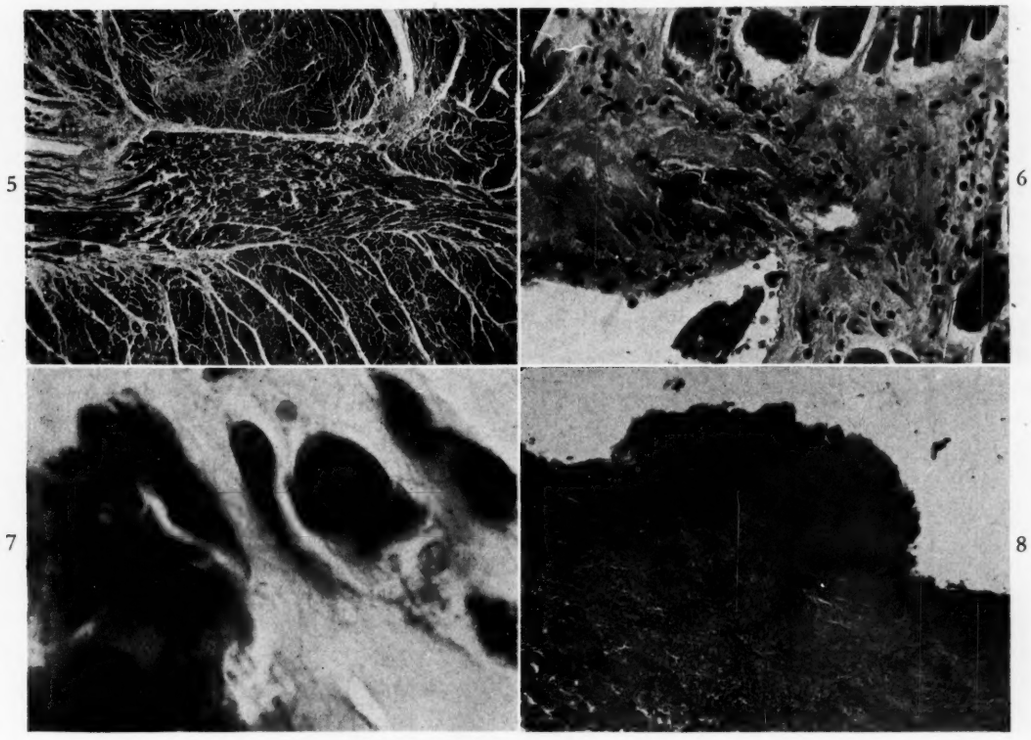

FIG. 5. A section of the myocardium from an area which was grossly interpreted as focal fibrosis. Note the loss of individual myocardial fibers and the replacement of groups of fibers by fibrous tissue.
FIG. 6. Another area of the myocardium showing the characteristic changes of fibrinoid degeneration and infiltration of inflammatory cells characteristic of an Aschoff body.
FIG. 7. High power view of the section in Figure 6 showing an Aschoff cell.
FIG. 8. Section of a verrucous vegetation on the endocardial surface of the left atrium.

A section of the aorta (Fig. 3) was taken to include the intima, media and adventitia from a region grossly thought to show syphilitic aortitis. The anatomic changes in the intima are the result of arteriosclerosis but another lesion is also present. In the media there are irregular, indistinct foci where the elastic tissue has been destroyed and has been subsequently replaced by fibrous tissue in which numerous small vessels are present. Some of the vessels are partially surrounded by lymphocytes and by an occasional plasma cell. Further, the adventitia is thickened by fibrous tissue and the vessels in the adventitia are thickened and irregularly surrounded by inflammatory cells such as those seen in the media. This lesion is characteristic of that seen in syphilitic aortitis. However, in the absence of an accompanying significant complication such as syphilitic valvulitis or stenosis of the coronary vessels, neither of which was present here, it is not possible to explain the cardiac hypertrophy on the basis of syphilitic infection.

A study of the microscopic changes in the liver (Fig. 4) gives evidence that the process which resulted in cardiac hypertrophy and subsequent decompensation was present sufficiently long that congestive cirrhosis of the liver developed. There is a diffuse increase in dense fibrous tissue throughout the portal regions and in some areas strands of fibrous tissue interlaced about individual isolated hepatic cells which are large and binucleated. In other areas broad bands of fibrous tissue surround hepatic cells grouped in lobule-like masses which contain no central vein. Some central veins are discernible, but most of these are surrounded by irregular foci of fibrous tissue which tend to extend along the sinusoids and join with the fibrous tissue in portal regions. There is infiltration with small and

large mononuclear cells which occasionally appear in small irregular groups of fifteen to twenty-five cells. The central veins and sinusoids in many instances are engorged with blood.

Turning to the heart, Figure 5 represents a section of the myocardium taken from an area interpreted grossly as exhibiting focal fibrosis. There is appreciable loss of myocardial fibers individually and in groups with subsequent replacement by moderately dense fibrous tissue. Occasionally the fibrous tissue is loose and edematous and a few lymphocytes and myocytes are scattered through the interstitium. In Figure 6 it is seen that in regions adjacent to certain blood vessels the collagenous fibrils are swollen and the collagen stains deeply acidophilic. Such a change is designated as fibrinoid degeneration and represents the initial stage in formation of an Aschoff body. Associated with such areas of degeneration in the interstitial tissue are irregular focal accumulations of round cells which are larger than lymphocytes but resemble them insofar as the nucleus is deeply basophilic and dense and the cytoplasm scant. Within such areas of inflammatory infiltration, minute foci of necrosis are observed in some instances. Frequently the large cells, which we know as Aschoff cells, are present (Fig. 7) within the nodular foci. These cells are characterized by an abundant amount of basophilic cytoplasm, the outline of which is irregular. The prominent nucleus is vesicular and contains a heavy bar-like nucleolus. In Figure 7 the nucleolus is indistinct but when one examines the section under the microscope and alters the focus, the character of the prominent hyperchromatic nucleolus can easily be made out.

Sections taken from the mitral valve showed the inner portions to be composed chiefly of altered collagen which was fragmented and deeply acidophilic. Especially at the base of the valve there were numerous lymphocytes, mononuclear cells, polymorphonuclear leukocytes and large irregular cells with abundant amphophilic cytoplasm and deeply basophilic nuclei. Throughout the valve there were several small blood vessels, a few of which were obstructed by partially organized thrombi. The endocardium covering the valve was slightly elevated by loose edematous fibrous tissue infiltrated with lymphocytes, larger mononuclear cells and a few polymorphonuclear leukocytes, some of which were eosinophiles. In Figure 8 one such section taken from the endocardial surface of the left atrium is shown. In a nodular focus, measuring 2 by 2 by 1 mm., the endocardium has been lifted by a mass of altered connective tissue elements which have undergone fibrinoid degeneration. At one point the endocardium is eroded and a thin layer of fibrin containing cellular débris is deposited over the surface. This lesion is characteristic of the verrucous endocarditis which is frequently observed during the course of acute rheumatic fever.

Within the limitations of our present knowledge, one may conclude that the Aschoff body, characterized by the distinctive features which have been enumerated, is found only in acute rheumatic fever. Investigation by various workers, among them Gross, indicate that the duration of Aschoff bodies in a rheumatic process is from four to six months and that after this period there is healing. In various sections taken from the heart of this patient different stages in the healing process could be found. Thus, in some areas there were fully developed characteristic Aschoff bodies whereas elsewhere less well defined nodular foci were noted in which the large irregular cells were becoming elongated and resembled fibroblasts. Finally, there were irregular foci where inflammatory cells were either minimal in number or were not present at all, and there was replacement of the myocardium by fully developed dense fibrous connective tissue. The latter changes represent the final changes in the recession and healing of the Aschoff bodies.

With respect to this patient, therefore, one may conclude that some years ago she had an attack of acute rheumatic fever

which subsequently receded and produced focal fibrosis of the myocardium. Following the initial stage at intervals which cannot be determined accurately, she had additional attacks of acute rheumatic fever, each of which added insult to the previously damaged myocardium resulting in hypertrophy of an advanced degree. Finally, within the last four to six months, as indicated by the presence of characteristic Aschoff bodies and well formed verrucae on the endocardial surface of the left atrium, the patient suffered still another attack of acute rheumatic fever which added more stress and strain to an already overworked heart. The terminal phase then was one of acute cardiac decompensation in a patient whose heart was markedly enlarged and unable to compensate for the damage incurred.

Anatomic Diagnosis: Acute rheumatic pancarditis; Aschoff bodies in the myocardium; verrucous endocarditis of the endocardium of the left atrium; focal fibrosis of the myocardium; fibrous thickening of the mitral and tricuspid valves and slight thickening of the chordae tendineae; fibrous adhesions between the cusps of the aortic valve and of the pulmonary valve; hypertrophy and dilatation of the heart (810 Gm.); moderate chronic passive congestion of the lungs, liver, kidneys, spleen and intestines; congestive cirrhosis of the liver; moderate acute bronchitis; syphilitic aortitis; slight chronic pyelonephritis.

Case Reports

Thiouracil Hepatitis*

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Toxic manifestations of thiouracil have been reported with increasing frequency as the use of this drug for the treatment of thyrotoxicosis has become more general. Agranulocytosis, leukopenia, drug fever, lymph node and glandular enlargement, skin reactions, edema of the feet, psychotic manifestations, albuminuria and hematuria have all been reported as directly due to thiouracil.[1–6] Gargill and Lesses[2] were the first to consider thiouracil a hepatotoxic agent. They reported two cases of jaundice in forty-three patients treated. The picture so simulated obstructive jaundice that a laparotomy was performed in one case but no obstruction was found. A biopsy of the liver was taken and it revealed the bile capillaries to be distended and empty in the outer half of the lobule and filled in the inner half. The central veins were prominent. The entire picture appeared to be one of acute biliary stasis and resembled the syndrome of postarsphenamine jaundice due to intrahepatic biliary tract obstruction.[6] Moore[1] reviewed 1,091 cases in which the patients were treated with thiouracil and mentions ten cases of lymph node or glandular enlargement in a total of 458 reporting the presence or absence of this complication. He mentions the occurrence of jaundice as a complication. In the discussion of this report Paschkis mentions two cases of agranulocytosis with evidence of jaundice and abnormal bromosulfphthalein retention. Recently Livingston and Livingston[7] reported agranulocytosis and hepatocellular jaundice secondary to propylthiouracil therapy.

The following case is presented as an instance of hepatitis secondary to thiouracil medication:

CASE REPORT

A twenty-seven year old colored female entered the hospital August 17, 1946, complaining of a mass in the neck and choking spells. She stated that she had noticed a gradually increasing fullness in the neck since the birth of her child two years previously. In spite of a ravenous appetite her weight had dropped from 123 to 93 pounds during this period. For the past year she had noticed increasing nervousness and fatigability. Her eyes began to bulge a few months prior to hospitalization. She also noticed some shortness of breath and edema of the feet. For three or four weeks prior to hospitalization there was a dry, non-productive cough but no hemoptysis. She had some dizziness and ringing of the ears. She had frequent attacks of diarrhea with ten loose stools a day. There was no history of melena or icterus.

The patient had irregular menses for the past year and amenorrhea since June, 1946. Her family history and past history were noncontributory.

Physical examination revealed an asthenic colored female with evidence of recent weight loss. The skin was warm and moist. There was moderate bilateral exophthalmus. The eye, ear, nose and throat examination was otherwise negative. There was a large non-nodular, diffuse, firm, bilateral enlargement of the thyroid gland. The chest was normal. There was no enlargement of the heart. There was a soft systolic murmur at the apex. The pulse rate was 110 and the blood pressure was 150/50. Examination of the abdomen was negative. There was slight pitting edema of both feet. Pelvic examination was essentially negative. The reflexes were equal and slightly hyperactive bilaterally.

The serum N.P.N. on August 19, 1946, was 41 mg. per cent and the total proteins were 7.6 Gm. per cent. The Kline and Kahn tests were negative. Urinalysis revealed a specific gravity of 1.014, a faint trace of albumin, was

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negative for sugar and had occasional hyaline casts, leukocytes and erythrocytes. The hemogram revealed a hemoglobin of 10 Gm., 64 per cent; red blood cells 3,600,000; white blood cells 5,650, with 56 neutrophiles, 37 lymphocytes, 5 monocytes and 2 eosinophiles. The serum cholesterol was 71.8 mg. per cent and the cholesterol esters were 26.7 mg. per cent. The basal metabolism rate was plus 71. The arm to tongue circulation time was 12 seconds. An electrocardiogram revealed a rate of 100, P-R interval of .16 second; a QRS interval .06 second. The P waves were prominent with sharp peaking of P_2 and P_3. The QRS axis was plus 80 degrees. The T_4 was deeply inverted. A roentgenogram of the chest revealed the heart to be slightly enlarged without characteristic configuration. The lung fields were clear. Views of the skull revealed the sella turcica to be within normal limits.

A diagnosis of thyrotoxicosis was made and it was decided to prepare the patient for surgery with thiouracil since propylthiouracil was not available at this time.

The patient was placed on a 4,500 calorie high protein diet, complete bed rest, phenobarbital 1 gr. three times a day, with a high intake of vitamins.

On August 20th the patient developed a severe follicular tonsillitis, with temperature elevation and cervical adenopathy. The swelling in the retrocervical region was so intense that a peritonsillar abscess was suspected but none was found. The leukocyte count was 5,300 with a normal differential. On August 21st she was placed on penicillin 30,000 units every three hours and this was continued for seventy-two hours. During this time the temperature dropped to normal and the tonsillar redness and swelling cleared. However, the cervical adenopathy persisted.

During a one-week observation period the pulse rate continued at about 100. She would also run an occasional temperature up to 101°F. She had gained 2 pounds in weight. On August 29th the patient was placed on thiouracil, .2 Gm. twice a day. Because of the exophthalmus she was also placed on thyroid, 1 gr. daily. The leukocyte count was checked three times weekly and varied from 3,000 to 7,850 with the majority of counts varying from 4,000 to 5,000. There was no change in the differential. No depression of the granulocytic series was found. The weight remained stationary and the temperature continued to spike between 98° and 101°F. daily but occasionally was up to 103°F.

The agglutination series revealed typhoid 'O' and 'H' positive 1:40, para B positive 1:40, B. abortus negative and Proteus OX19 positive 1:40. Stool cultures were negative for E. typhi. There had been moderate improvement clinically. The basal metabolism rate on September 19th was plus 14.

On September 16th (eighteen days after the start of thiouracil therapy) the patient developed slight jaundice. The icterus index was found to be 33.6 units. Because of the possibility that thiouracil might be causing the jaundice, the drug was immediately discontinued. A blood fragility test in the patient revealed hemolysis beginning at .42 per cent and not complete at .24 per cent, while a control started at .44 per cent was complete at .32 per cent. The serum cholesterol on September 23rd was 148 mg. per cent. The urine was negative for urobilinogen. A diagnosis of hepatitis was made and the patient was placed on a high carbohydrate, high protein, low fat diet with infusions of glucose, with methionine 1 Gm. three times a day. The thyroid extract was discontinued on September 18, 1946.

The temperature now varied from 98.6° to 99.4°F. daily with only rare spikes to 100°F. The pulse varied from 70 to 100. Supportive treatment for hepatitis was continued but the icterus index gradually rose. The van den Bergh test was immediate and direct on October 4, 1946. The serum cholesterol was 161.9 and cholesterol esters were 71.3 on October 11th. The prothrombin time was 82 per cent of normal and the icterus index was 96.5 units on October 17th. The cephalin-cholesterol flocculation was 2 plus; total proteins 7.7 Gm. per cent with albumin 3.4 Gm. per cent and globulin 4.3 Gm. per cent. The N.P.N. was 27 mg. per cent. The urine was repeatedly negative for urobilinogen. The stool was negative for urobilinogen on October 19th. The oral hippuric acid liver function test revealed .80 Gm. excreted in one hour. The jaundice became so intense that a common duct stone was considered. A cholecystogram on October 23rd revealed nonvisualization of the gallbladder.

The lymph nodes became generally palpable on October 5th and the possibility of a generalized reticuloendotheliosis was considered. Biopsy of a cervical node was done

and was reported to show simple hyperplastic lymphadenitis.

On October 26, 1946, the patient developed paranoid tendencies. The liver became palpable; the spleen became questionably palpable. The leukocyte count dropped to 2,000 after thiouracil was discontinued and remained between 3,000 to 5,000/cu.mm. The differential was normal. The hemoglobin dropped to 8.3 Gm. and the patient was given blood and plasma. On August 30th the icterus index was 130. The patient expired on November 13, 1946.

The temperature had maintained a low rise from 98° to 99.6°F. daily during the last few weeks of her illness and rose to 104°F. prior to her death. The pulse varied from 80 to 100 but rose to 160 prior to death. Her respirations were 20 but rose to 34.

Postmortem Examination. The autopsy revealed an emaciated colored female who appeared to be about the stated age. The sclerotics were rather deeply jaundiced and there was sordes of the lips and tongue. The thyroid was diffusely enlarged both to palpation and inspection. The cervical lymph nodes were palpable. The breasts were atrophic and the abdomen was scaphoid. There was a superficial bed sore in the sacral region. The external genitalia appeared normal and the thighs and legs were symmetrically equal and free from pitting edema. The subcutaneous adipose tissue was very scant.

The pleural cavities were free from adhesions and fluid. The right lung weighed 500 Gm. and the left 360 Gm. The right upper lobe was firmer than normal and the pleura over the dependent aspect of the upper and lower lobes was dark red and glistening. Section revealed areas of dark red consolidation measuring from 1 to 2 cm. in the dependent portions of both the upper and lower lobes, and moderately diffuse edema. The left lung showed dependent congestion and edema. The bronchi contained a little mucus and froth and showed yellowish-red lining. The peribronchial lymph nodes were moderately enlarged and black and a calcified node was present on each side. The pericardial layers showed a yellowish tint and the sac contained approximately an ounce of clear yellowish fluid. The heart weighed 290 Gm. and was conical in shape. The right ventricle was moderately dilated and its wall measured .5 cm. in thickness. The myocardium was dark red, wet, of normal consistency and free from gross scars. The valve leaflets showed an icteric tint. The coronary ostia and arteries showed no evidence of disease. The lining of the aorta was smooth and light yellow. Thy thyroid was symmetrically enlarged and weighed 90 Gm. The fissures of lobulation on its external surface were accentuated and the capsular blood vessels were prominent. The cut surfaces were brownish-red and opaque. No nodules were present.

The base of the tongue showed considerable nodular irregularity due to hyperplasia of lymphoid tissue. The left tonsil was enlarged and somewhat pedunculated. The superficial and deep cervical lymph nodes on the right were enlarged, soft and pink. The thymus weighed 20 Gm. and was salmon-pink in color. The larynx and trachea appeared normal other than slightly icteric. The lining of the esophagus was smooth and showed a yellowish tint. The stomach was of average size and its lining was mottled gray and pink. The small and large intestines showed nothing noteworthy.

The mesenteric lymph nodes measured as much as 1 cm. in diameter and in some instances showed purplish color. The pancreatic and hepatic nodes were moderately enlarged and of a brownish red color. The retroperitoneal lymph nodes were not enlarged. The peritoneum was of a grayish pink color, dry and free from adhesions. The spleen was free from adhesions and weighed 120 Gm. Surfaces made by section were grayish red, moderately soft and the malpighian bodies were distinct but not large. The liver weighed 1,080 Gm. and slight shallow fissuring was noted on the anterior surface of the right lobe just above the lower edge. However, definite nodulation was not present. The capsular surface tended toward an olive-green color. Surfaces made by section were brownish red with a greenish tint, and the lobular etching was fairly distinct. The extrahepatic bile ducts and gallbladder showed nothing noteworthy. The pancreas weighed 90 Gm. and was grayish pink in color. Section revealed distinct lobular architecture. The adrenals had a combined weight of 18 Gm., the left being a little larger than the right. The cortices were of regular and average thickness and were yellowish red in color. The medullae were soft and brownish red. The kidneys were of about equal size and had a combined weight of 290 Gm. Their capsules stripped easily exposing smooth brownish red surfaces. The cut surfaces showed a similar color, were moist and glistening and the archi-

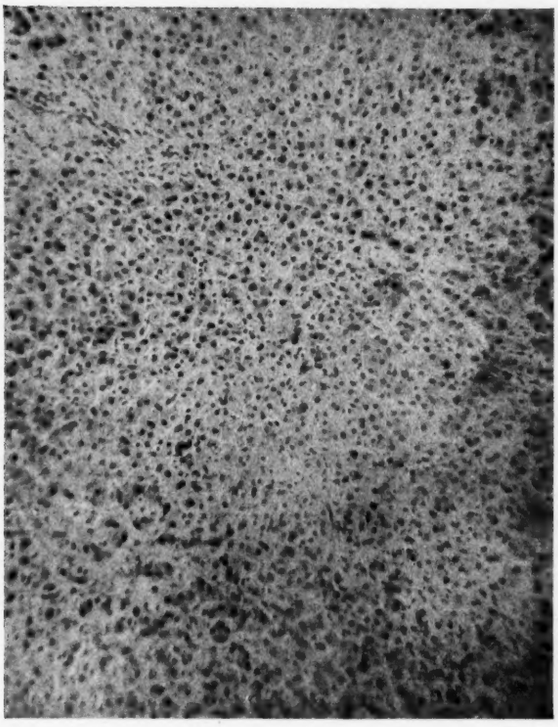

FIG. 1. Section of liver showing area of focal necrosis.

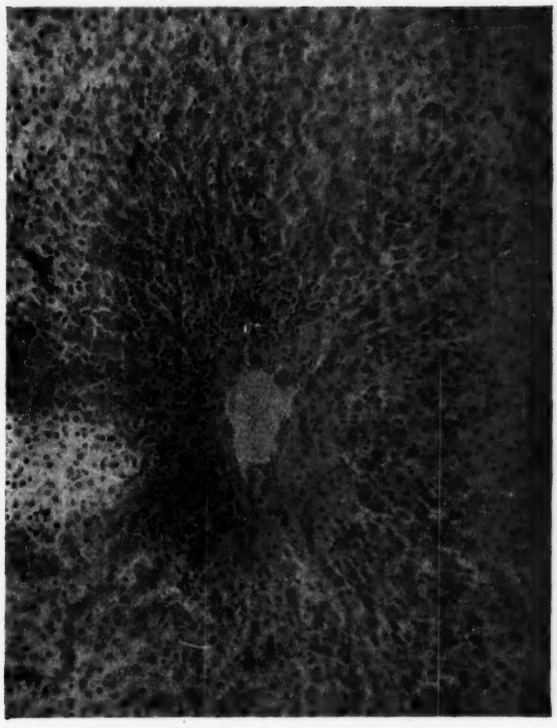

FIG. 2. Section of liver showing central necrosis, with hyaline thickening of the central vein wall with necrosis, disorganization and some cellular infiltration of the hepatic cells.

tectural features were fairly distinct. The renal pelves, ureters and urinary bladder showed nothing noteworthy. Other than erosion of the cervix, the uterus and adnexa showed no noteworthy change.

The marrow in the sternum and lumbar vertebrae was brownish red in color and in the sternum it was soft. The brain and meninges were negative for gross lesions.

The microscopic examination of the thyroid showed marked epithelial hyperplasia, reduction of the colloid but no lymphoid hyperplasia. The epithelium was tall and columnar and showed numerous papillary infoldings into the acini. The colloid stained poorly, contained desquamated epithelial cells and showed marginal vacuolization. Moderate diffuse fibrosis of the myocardium was noted in the sections from the heart. Sections from the consolidated areas of the right lung revealed a purulent exudate in the bronchi and surrounding alveoli. In sections not showing an inflammatory reaction the alveoli were filled with a pink-staining, homogeneous fluid. In addition to old fibrocaseous tuberculosis of the peribronchial lymph nodes an occasional fresh tubercle with a necrotic center was noted. The sections from the enlarged cervical and abdominal lymph nodes revealed distention of the sinuses with endothelial cells associated with a sprinkling of leukocytes (sinus catarrah).

The spleen was congested and showed moderate reticulosis and infiltration by polymorphonuclear leukocytes and plasma cells. The germinal centers of some of the follicles were necrotic. Fibrosis (mainly interlobular) and focal postmortem necrosis was noted in the pancreas. The thymus was hyperplastic for this age. The sections from the kidneys revealed fairly extensive calcification of the lower portion of the collecting tubules. There were also bile casts and degenerative changes of the tubular epithelium.

The liver showed both focal and central necrosis. (Figs. 1 and 2.) The center of almost every lobule presented a rarefied disorganized appearance, indicating disappearance of hepatic cells. Many of the remaining central cells exhibited karyolysis and pyknosis. Slight polymorphonuclear leukocytic infiltration was frequently observed in the central areas. Endophlebitis of the central and sublobular veins was fairly widespread. This was frequently represented by hyaline thickening of the walls of the veins but not infrequently an earlier stage was

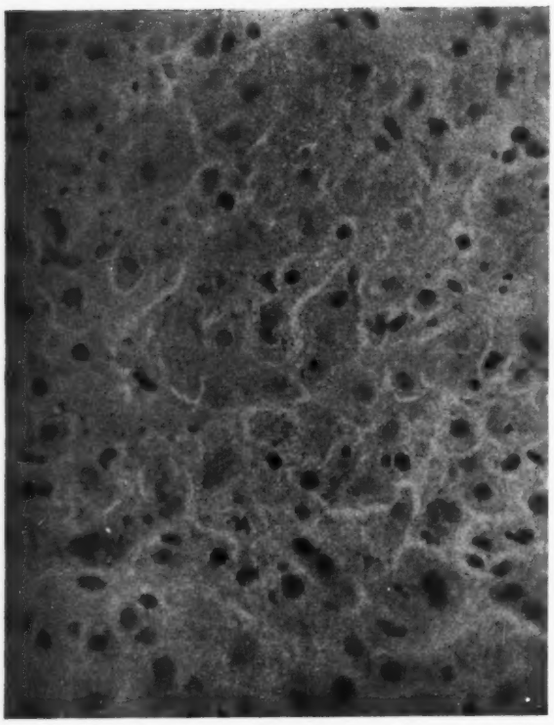

FIG. 3. High power from central zone showing so-called "bile casts" and necrobiosis.

encountered, characterized by swelling and proliferation of the endothelial cells and slight cellular inflammatory reaction. Central bile pigmentation (hepatic cells laden with a greenish yellow pigment) and plugging of the bile canaliculi centrally by so-called bile casts were much in evidence. (Fig. 3.) Rarely one encountered small foci of necrosis in the midzone of the lobule which might or might not be contiguous with an area of central necrosis. In the subcapsular region an irregular pattern of scarring interpreted as residual to more remote hepatic injury was encountered.

In places, chiefly in the zona reticularis, the adrenals showed a disorganized appearance with loss of the parenchymal cells and consequent prominence of the scaffolding element. The sections from the brain, bone marrow, uterus and adnexa showed no noteworthy change.

The anatomic and microscopic diagnoses were exophthalmic goiter, bronchopneumonia, slight hypertrophy and fibrosis of the heart, calcified, fibrocaseous and miliary tuberculosis of the peribronchial lymph nodes, simple lymphadenitis (sinus catarrah) of the cervical and abdominal nodes, moderate acute hyperplasia of the spleen, hyperplasia of the thymus, fibrosis and focal postmortem necrosis of the pancreas, necrobiotic change in adrenals, focal and central necrosis of the liver associated with area of fibrosis in the subcapsular region, bile nephrosis and metastatic calcification of kidneys and jaundice.

COMMENT

The hepatic damage in this case could be due to both the thyrotoxicosis and the thiouracil. However, it is doubtful that it was due to the former because the jaundice occurred when the toxemia associated with thyrotoxicosis was decreasing, as shown by the falling basal metabolism rate and general clinical improvement. Since no other hepatotoxic substance was administered, it is concluded that the thiouracil was the etiologic factor. Although this is a rare complication of thiouracil therapy, it must be considered an important one. The patients in the cases previously reported have recovered. However, this patient was in such a severely debilitated state that she was unable to survive in spite of general supportive measures.

SUMMARY

A case of hepatitis which occurred subsequent to thiouracil is presented, with autopsy findings.

REFERENCES

1. MOORE, FRANCIS D. Toxic manifestations of thiouracil therapy. *J. A. M. A.*, 130: 315, 1946.
2. GARGILL, SAMUEL L. and LESSES, MARK FALCON. Toxic reactions to thiouracil. *J. A. M. A.*, 127: 890, 1945.
3. WILLIAMS, ROBERT H., CLUTE, HOWARD M., ANGLEM, THOMAS J. and KENNEY, FRANCIS R. Thiouracil in the treatment of thyrotoxicosis. *J. Clin. Endocrinol.*, 6: 23, 1946.
4. NEWMAN, ELLIOT V. and JONES, BENJAMIN F. Agranulocytosis from thiouracil. *J. A. M. A.*, 132: 77, 1946.
5. LIMARZI, L. R. and RICEWASSER, H. Thiouracil granulocytopenia and sternal marrow examination. *Am. J. Clin. Path.*, 16: 306, 1946.
6. HANGER, FRANKLIN M. and GUTMAN, A. B. Postarsphenamine jaundice apparently due to obstruction of intrahepatic biliary tract. *J. A. M. A.*, 115: 263, 1940.
7. LIVINGSTON, HAROLD J. and LIVINGSTON, SAUL F. Agranulocytosis and hepatocellular jaundice. *J. A. M. A.*, 135: 422, 1947.

Rupture of Splenic Infarct and Sudden Death Complicating the Course of Subacute Bacterial Endocarditis*

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RUPTURE of a splenic infarct from any cause is rare. Blumer[1] in 1923 reported a series of 150 autopsies in patients dying of subacute bacterial endocarditis in which there were 115 splenic infarcts. Of these infarcts, sixteen were septic in character. No mention was made of rupture of any of these splenic infarcts. Todd[2] in 1919 described a case of ruptured splenic infarct, with resultant hemorrhage and death. The etiology in this case was a gunshot wound of the leg, with an infected compound fracture complicated by septic embolism of the spleen. Billings[3] in 1929 reported a case of splenic abscess of unknown origin which caused generalized peritonitis and death by rupture into the peritoneal cavity. Wolfson[4] in 1944 stated that when abscess of the spleen occurs as a complication of subacute bacterial endocarditis, operation is contraindicated because of the grave prognosis of the underlying disease.

The first case of rupture of the spleen in the course of subacute bacterial endocarditis was cited by Lake et al.[5] in 1919. In this case ulceration through the splenic artery had occurred. Vallee,[6] also in 1919, described a case. In 1926 Krokiewicz[7] attributed rupture of the splenic infarct in his case to paroxysmal increases of blood pressure when the patient strained at stool. Pallasse et al.[8] in 1931 attributed death in their case to rupture of a hemorrhagic splenic infarct. Braxton-Hicks[9] in 1932 described a fifteen year old girl who at autopsy showed no evidence of splenic infarction. However, there was marked necrosis of the lower half of the spleen, with rupture through the capsule. The case of Kerkhof et al.[10] in 1933 was that of a seventeen year old boy. Death here was also due to ruptured splenic infarct and subsequent hemorrhage. Willius[11] in 1935 described a twenty-three year old male whose exitus was prompted by rupture of a mycotic aneurysm of the splenic artery. Fingerland[12] in 1938, Rantz et al.[13] in 1943, Mallory[14] in 1946 and Hertzog et al.[15] also in 1946 reported similar cases of subacute bacterial endocarditis, with rupture of the spleen and subsequent death.

There are many reports of spontaneous rupture of the spleen due to causes unknown as well as to definite etiologic factors. There are also many case reports of splenic infarction, with or without abscess formation, in which the spleen did not rupture. However, a careful perusal of the medical literature to date reveals only eleven case reports of subacute bacterial endocarditis complicated by rupture of the spleen. The following case is cited as an addition to this group:

CASE REPORT

E. J. was first admitted April 28, 1946. In February, 1946 this twenty-seven year old white male had some teeth extracted while he was suffering from the "grippe," and was running a slight temperature. Two weeks later he noted onset of chills, fever, sweats and loss of appetite.

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These symptoms became progressively worse, finally reaching the point at which he was incapacitated. He then consulted his physician who examined him and promptly took a blood culture. The blood culture was positive for streptococcus viridans on April 28th and the patient entered the hospital for treatment of subacute bacterial endocarditis.

Past history revealed that the patient had been a normal baby at birth. He had the usual childhood diseases plus tonsillitis in infancy. His tonsils were removed at an early age. There was no history of scarlet fever, rheumatic fever, growing pains or frequent sore throats. He had never experienced a serious illness and was active in athletics in high school. His occupation was that of a machinist.

Family history was completely negative. No familial tendencies were elicited.

Review by systems was essentially negative, except for the present illness.

Physical examination on admission showed the patient to be a well developed, well nourished white male, not cyanotic or dyspneic, but appearing feverish and somewhat dehydrated. The skin was clear. No petechiae were noted. The head was essentially negative. The pupils were round, regular and equal and reacted to light and accommodation. There was no scleral icterus. The ears were negative to external examination. The nasopharynx was clear. A few teeth were missing and the remaining ones were very carious. The thyroid was not enlarged, and there was no palpable adenopathy or venous distention. The chest was clear to percussion and auscultation. The heart was enlarged to the left and down. No thrills were noted. There was a harsh, blowing systolic murmur heard best at the third and fourth interspaces to the left of the sternum and transmitted to the base and left axilla. Occasional extrasystoles were heard. The blood pressure was 180/80. Examination of the abdomen revealed no palpable organs or masses, no tenderness, spasm or hernias. Examination of the genitalia was negative, and the rectal examination was not significant. There was no cyanosis, clubbing or edema of the extremities. The peripheral pulse was regular, except for occasional dropped beats.

Laboratory results on admission were as follows: Red blood cells, 4,100,000, with a hemoglobin concentration of 78 per cent; white blood cells, 7,800, with 80 per cent neutrophiles, 18 per cent lymphocytes and 2 per cent monocytes. Non-protein nitrogen was 33.7 mg. per 100 cc., and the fasting blood sugar was 111 mg. per 100 cc. The urine was acid, with a specific gravity of 1.023, and was negative for albumin, sugar, red blood cells and casts. The blood culture was positive on April 28th for streptococcus viridans.

Diagnosis of subacute bacterial endocarditis was made, and congenital heart disease, potentially cyanotic in type, probably an interventricular septal defect, was considered.

The patient was put on a regimen of 50,000 units of penicillin, intramuscularly every four hours, and ½ Gm. of sulfadiazine orally every four hours, with sufficient sodium bicarbonate to keep the urine alkaline. This was continued until June 8th, after which the penicillin was administered in 1,000 cc. of 5 per cent glucose in water, 1,000,000 units daily. This was kept up until July 1st even though the blood culture was reported negative on June 18th. A total of 36,300,000 units of penicillin was administered during this admission.

During his hospital stay the patient developed what was thought to be a patchy type of bronchopneumonia in the face of all the medication he received. This process gradually subsided. His temperature curve was septic in type for the first five days, and then gradually dropped to between 99°F. and 100°F., at which level it hovered for the next six weeks, with daily spikes. The temperature slowly returned to normal toward the end of his hospital stay. He was discharged on July 1st markedly improved.

After one week at home the patient noted return of his previous symptoms and even though the blood culture was still negative, entered the hospital on July 21, 1946 for further intensive treatment. This time he received 1,000,000 units of penicillin daily, in 1,000 cc. of normal saline by intravenous drip, from July 21st to August 19th. That made a total of 30,000,000 units of penicillin for this admission.

Although his admission temperature was only 100°F., he ran a spiking course similar to his previous admission, gradually returning to a normal temperature a few days before discharge. The symptoms gradually subsided and no new symptomatology was noted. A chest x-ray on August 6th showed evidence of an old left hilar infarction in the same area that the pneumonia was thought to have occurred.

The interval between the second and third

admissions was three weeks during which the patient again noted onset of the previous chills, fever, anorexia and sweating. The blood culture was again positive on September 10th and he entered the hospital for the third time for further intensive treatment.

The physical examination was essentially unchanged from those on former admissions, except for the heart. There were still no petechiae, no enlarged nodes or organs. The cardiac findings had changed somewhat. At this time the patient had a harsh systolic murmur over the whole precordium, heard best in the fifth interspace to the left of the sternum. The second sound was replaced by a diastolic murmur, heard over the whole precordium but best heard over the aortic area. The blood pressure was 150/80 in both arms and 225/85 in the legs. The laboratory results were not significantly changed. At no time was there any hematuria, gross or microscopic.

Penicillin was once again begun, at the rate of 2,000,000 units a day, in 1,000 cc. of normal saline intravenously. It was stopped on September 29th because the blood culture had turned negative. The blood culture again became positive on October 10th, and penicillin was once more started in the same dosage until October 31st. Penicillin was then discontinued until November 11th when a dosage of 3,500,000 units a day was administered in 2,000 cc. of normal saline intravenously for the next five days. It was then stepped up to 5,000,000 units daily for the following five days.

Several penicillin blood levels were taken during the last admission, and the concentration ranged from 0.124 to 4.0 units per cc. Penicillin resistance studies were also made, and the smallest inhibiting amount of penicillin ranged from 0.0625 to 0.5 units per cc. of blood.

During the last week of his illness the patient complained many times of pain in the left upper quadrant of his abdomen which he described as sharp, transient, non-radiating in nature. Physical examination revealed tenderness in this region but the spleen was never definitely palpable. On the evening of November 20th the patient was suddenly seized with severe pain in the left upper quadrant, radiating to the groin, with a sense of fullness in the abdomen. He immediately developed marked respiratory distress, became clammy and pulseless, with an unobtainable blood pressure. In a matter of minutes he went into irreversible shock despite supportive therapy and expired.

The penicillin dosage during this admission was 122,500,000 units. The total dosage for his entire illness was 188,800,000 units of penicillin.

Autopsy report revealed the following: The body was that of a well developed, well nourished, very pale white male. The pupils were round and equal and there were no conjunctival petechiae. A 5 cm. transverse scar was noted just below the left patella. There were no cutaneous nodules or petechial hemorrhages present on the body. There were a few dense adhesions in both pleural spaces. These were most marked in the apical and midportions of the lung. There was no free fluid. About 10 cc. of straw colored fluid was noted in the pericardial cavity; no adhesions were present. On exposing the peritoneum a dark red appearance was noted. Palpation through the peritoneum revealed the presence of a large amount of fluid. On opening the peritoneum about 4,000 cc. of semiclotted blood was noted. The omental bursa was completely filled with clotted blood. The greater omentum was swung to the left upper quadrant of the abdomen where it had formed a nearly complete envelope about the spleen. The very dense adhesions through this quadrant made the spleen difficult to dissect. The heart weighed 525 Gm. There was both dilatation and hypertrophy; hypertrophy was present in both ventricles, more marked in the left. Dilatation was marked and was confined to the right auricle. The left ventricle measured 30 mm. in thickness and the right measured 18 mm. The right auricle measured 3 mm. in thickness and the left measured 1.5 mm. The orifice of the tricuspid valve was enlarged admitting four fingers with ease. There was thickening and shortening of the chordae tendinae of this valve. Most of the pathologic condition was confined to the mesial leaf of the tricuspid valve. On the atrial surface there were three small, pink, fresh, friable vegetations which could be easily scraped away. These extended up on to the endocardium of the right auricle. There was a foramen on the atrial surface of the mesial leaf of the tricuspid valve measuring 0.4 cm. in diameter. (Fig. 1.) This foramen led down to a pocket, the bottom of which communicated directly with the left ventricular cavity at about the level of the mitral valve, thus forming an interventricular septal defect. The ventricular septum itself in

FIG. 1. The right side of the heart, with vegetations present on the tricuspid valve and the opening of the interventricular septal defect into the mesial leaf of the tricuspid valve.

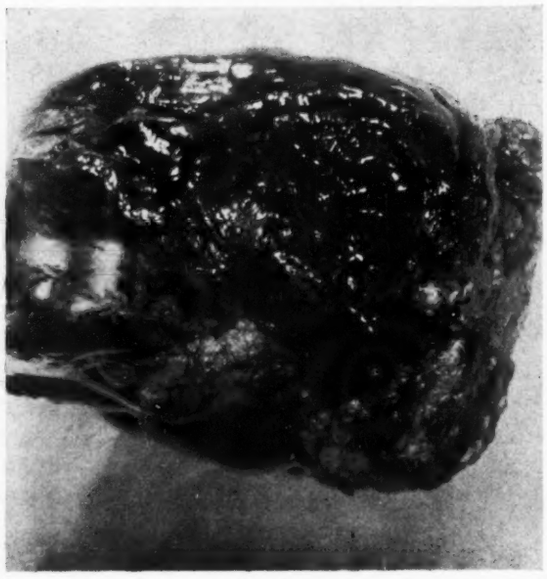

FIG. 2. The spleen, with a large area of rupture and evidence of both old and recent infarction.

this area was thickened and fibrous. The mitral and pulmonary valves were free from disease while the aortic valve revealed small, pink, friable vegetations on the noduli Arantii of all the cusps. There was fusion of one aortic commissure. The myocardium revealed only the hypertrophy previously described. The right lung weighed 320 Gm., and the left weighed 310 Gm. The external surface of both lungs was not unusual, except for a purplish color confined to both lower lobes. Crepitation was absent. Section revealed an obliteration of lung markings in these areas, with replacement by a homogeneous purple color. The liver weighed 1,875 Gm. It was markedly enlarged. It was dark red in color and soft in consistency. Section revealed a nutmeg appearance. The gallbladder and ducts were free from calculi. The spleen weighed 875 Gm. It was swollen, with a tense capsule and its edges were rounded. On exposing the renal surface of the spleen a massive defect was noted, measuring 11 by 7 cm., the depth being best appreciated by the fact that a finger inserted into this defect touched the diaphragmatic surface of the spleen with ease. The diaphragmatic surface was covered with varying sized, rather firm, greyish patches, ranging from 0.5 cm. to 4.5 cm. in diameter. There appeared to be marked variation in the age of these infarcts. Section of the spleen revealed that these areas were found in some cases to extend as far as 3 cm. into the splenic substance where they formed a cavity filled with purulent material. Most of the splenic parenchyma, especially in the vicinity of the rupture, was soft and mushy and apparently without structure. No abnormalities were found in the gastrointestinal tract, pancreas, kidneys or adrenals.

The myocardial fibers of the heart were mildly hypertrophied. Among them was a single tiny group of polymorphonuclear and mononuclear cells. No Aschoff bodies were seen. Sections of the tricuspid valve showed fibrous thickening and vascularization. There was a low, broad vegetation composed of granulation tissue covered by fibrin and necrotic débris. Beneath the surface were two small calcific deposits. Gram stain revealed a few gram-positive cocci in short chains in two vegetations. There was mild fibrous thickening of some alveolar septa in the lung. There was mild sinusoidal engorgement around the efferent veins of the liver, with increased yellow pigmentation of cells in those regions. In the spleen there were areas of old and recent infarction and some small suppurative infarcts. One large, fresh infarct was hemorrhagic and extended through the capsule. (Fig. 2.) One artery was filled with necrotic débris containing a calcium deposit. A smaller adja-

cent vessel contained a fresh thrombus. No abnormalities were found in the pancreas, adrenals or kidney.

Anatomic Diagnosis: Congenital cardiac anomaly; patent interventricular septum; rheumatic heart disease, inactive; tricuspid and aortic valvulitis; tricuspid insufficiency; cardiac hypertrophy and dilatation; subacute bacterial endocarditis; septic infarcts of the spleen; rupture of the spleen; hemoperitoneum; bilateral atelectasis; chronic passive congestion of the liver.

SUMMARY

1. A review of the medical literature to date revealed only eleven cases of subacute bacterial endocarditis which were complicated in their course by rupture of the spleen and consequent death.

2. A report of another such case is presented in which the mechanism of death was massive internal hemorrhage.

Acknowledgment: The author wishes to express his thanks to Dr. V. M. Maddi from whose private service this case report was taken.

REFERENCES

1. Blumer, G. Subacute bacterial endocarditis. *Medicine*, 2: 105, 1923.
2. Todd, A. H. A case of septic infarct of the spleen; causing rupture of the spleen, hemorrhage, and death. *Brit. J. Surg.*, 6: 467, 1919.
3. Billings, A. E. Abscess of spleen. *Ann. Surg.*, 88: 416, 1928.
4. Wolfson, I. F. Abscess of the spleen. *New England J. Med.*, 230: 135, 1944.
5. Lake, N. C., Kevin, H. K. and Irel, S. Internal hemorrhage from splenic infarct. *Lancet*, 2: 13, 1919.
6. Vallee, A. Multiple infarcts of the spleen in malignant endocarditis; rupture of the spleen and peritonitis. *Canad. M. A. J.*, 9: 1064, 1919.
7. Krokiewicz, A. Spontanruptur der Milz bei Endocarditis ulcerosa aortica. *Virchow's Arch. f. path. Anat.*, 262: 328, 1926.
8. Pallasse, E., Gueclaich, A. and Chapius, A. Spontaneous hemorrhage and capsular rupture in infectious endocarditis. *Lyon méd.*, 147: 577, 1931.
9. Braxton-Hicks, J. A. Death from rupture of infarcted spleen in case of malignant endocarditis. *Brit. M. J.*, 2: 351, 1932.
10. Kerkhof, A. C. and Giere, E. K. Rupture of splenic infarct in subacute bacterial endocarditis. *Am. Heart J.*, 8: 423, 1933.
11. Willius, F. A. Clinic on subacute bacterial endocarditis. *Proc. Staff Meet., Mayo Clin.*, 10: 73, 1935.
12. Fingerland, A. Rupture of spleen in patient with endocarditis lenta. *Casop. lék. česk.*, 77: 422, 1938.
13. Rantz, L. A. and Kirby, W. M. M. Enterococcic infections. An evaluation of the importance of fecal streptococci and related organisms in the causation of human disease. *Arch. Int. Med.*, 71: 516, 1943.
14. Mallory, T. B. Clinical pathological conference. *New England J. Med.*, 234: 634, 1946.
15. Hertzog, A. J., Nesse, G. and Vandersleuis, C. Subacute bacterial endocarditis with rupture of spleen. *Minnesota Med.*, 29: 791, 1946.

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Complications of Deep X-ray Therapy of Carcinoma of the Lung*

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THE effect of high voltage roentgen irradiation on the human lung has been studied chiefly in connection with the palliative treatment of intrapulmonary extension or metastasis from breast carcinoma. There has usually been abundant clinical material of this nature available, partly due, no doubt, to the fact that there still exists a school of surgical thought believing that radical breast surgery is useless, that just as good results can be obtained after simple mastectomy by turning the patient over to the roentgenologist who is supposed to irradiate and kill any cancer cells remaining in the axilla, pectoral muscles or mediastinum. Such surgeons by this escapist attitude toward the problem are probably harming not only their patients but also the entire cause of adequate cancer therapy. It has been possible, however, from this and other sources to obtain material for the study of x-ray reactions in human tissues, such as is found in the papers of Leach, Farrow, Foote and Wawro,[1] Leach[2] and Widmann,[3] and these will be referred to later in more detail.

In 1940 I reported a study[4] of a case of a patient with bronchial adenocarcinoma who had received excessive doses of roentgen rays thereby producing a pneumonitis and pleuritis typical of an irradiation reaction. This effect was extensive and severe enough to lead to the death of the patient although the neoplasm remained local, as it was well walled-off by fibrous tissue. The purpose in publishing the case was to draw attention to the dangers of roentgen rays, especially when administered by different operators each giving courses of treatment without knowing what previous exposures had been incurred. The cumulative effect of such irradiation in this instance caused irreparable damage to lung tissue and resulted in a fatality. Postmortem material of this nature has been and apparently still is uncommon, so another case of primary carcinoma of the lung with complicating roentgen ray reactions in pleura and lung is offered with complete autopsy findings. It is also another illustration of local control of a bronchial (squamous cell) carcinoma by the rays with, at the same time or subsequently, tissue insult far removed from the tumor itself contributing to the fatal outcome.

CASE REPORT

The patient was a white man, forty-nine years of age, who had been under the care of Dr. James V. Barrett of Troy, N. Y., for a chronic cough of eight months' duration. He complained of loss of appetite, strength and weight, and a chestache not definitely localized. There was little sputum, no lymphadenopathy and no known contact with tuberculosis. Dizziness, hoarseness and night sweats had been present for several months. He entered the Pawling Sanatarium on July 18, 1940. At that time his state of nutrition was fair. The only pulmonary signs were inconstant râles in the left lung posteriorly. A roentgenogram then showed a mass at the right hilum, ? tumorous. (Fig. 1.) The descending bronchial trunks were accentuated but there was no parenchymal disease present. A bronchoscopic examination was made on August 7, 1940, and no tumor, either intra- or extrabronchial, was demonstrable. There was no apparent bronchial stenosis but at the tip of the carina there were two areas of redness.

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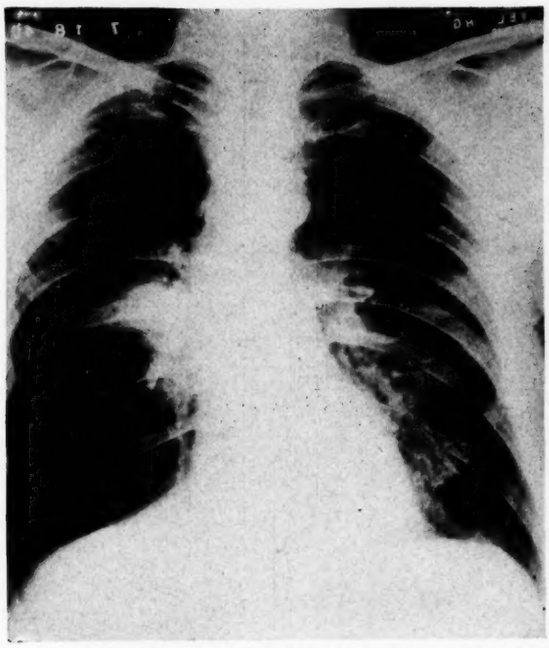

FIG. 1. Chest film July 18, 1940, showing a tumor mass in the region of the right hilum.

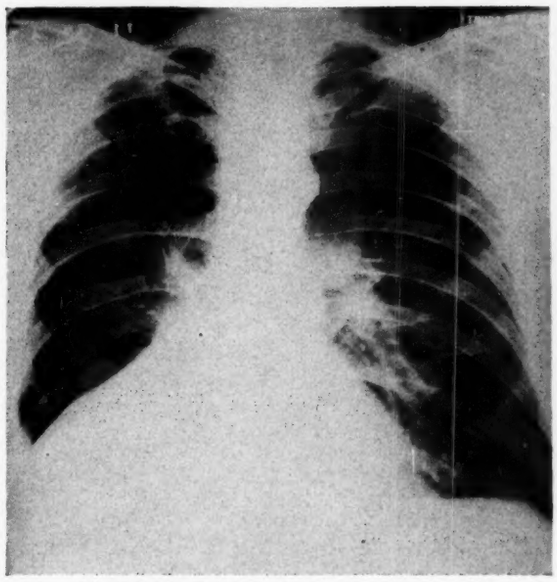

FIG. 2. November 13, 1941, an area of increased density at the right hilum. The descending bronchial trunks are markedly dilated on the right side and are surrounded by flocculent shadows of inflammatory character. A wedge-shaped area of density extends from the hilum to the base which is typical of atelectasis.

On November 6, 1940, he was improved in a general way, and a roentgenogram of the chest showed that the mass noted previously at the right hilum was greatly reduced in size and more indefinite in outline. There was, however, slight mottling in the mid-zone of the right lung. On March 20, 1941, there was no change in the clinical picture, but x-ray showed a wedge-shaped area of density proceeding from the hilum to the base, suggesting atelectasis in the right lower lobe. In May, 1941, he began to have cyanosis and there was dullness with absence of breath sounds throughout the right lung. A roentgenogram showed complete collapse of the right lung and the heart pulled slightly to the right. The finger nails were becoming curved and cyanotic. Cervical lymphadenopathy was detected for the first time. There were frequent cardiac extrasystoles. Blood pressure was 98 systolic and 60 diastolic. Bronchoscopic examinations in April, June and December, 1941 did not reveal any lesion. In December, 1940, a small amount of secretion was seen coming from the right middle bronchus. Sputum examinations were always negative for acid-fast bacilli, but from June to December, 1941, sputum smears and cultures were positive for monilia. Cultures on Petroff's and Dorset's media of material from bronchial aspirations were negative for tubercle bacilli after three months of incubation. There had been no rise of temperature. The pulse rate varied between 90 and 112. Atelectasis in May, 1941, with pneumothorax caused marked dyspnea but the lung gradually inflated and breathing became normal. In July, 1941, hematuria developed. The prostate was found greatly enlarged. An intravenous pyelogram was normal. By August, 1941, his general condition was greatly improved. There was less coughing, and no further hematuria. A roentgenogram of the chest no longer revealed any abnormal shadow in the right hilum. There were a few scattered, moist râles in the right posterior mid-zone. Whatever the nature of the condition it was agreed by all observers that it was not clinical tuberculosis.

On October 2, 1941, his temperature was 99°F., pulse 104 and respirations 24. Râles were heard at the extreme right base posteriorly. A chest film showed an area of increased density in the right hilum. The descending bronchial trunks were markedly dilated on the right side and were surrounded by flocculent shadows. The right costophrenic angle was obscured. A diagnosis of bronchiectasis and probable new growth in the right lower lobe was made. Three weeks later he complained of much chest pain, and a roentgenogram revealed again a wedge-shaped area of density which was probably atelectasis in the right lower lobe. (Fig. 2.)

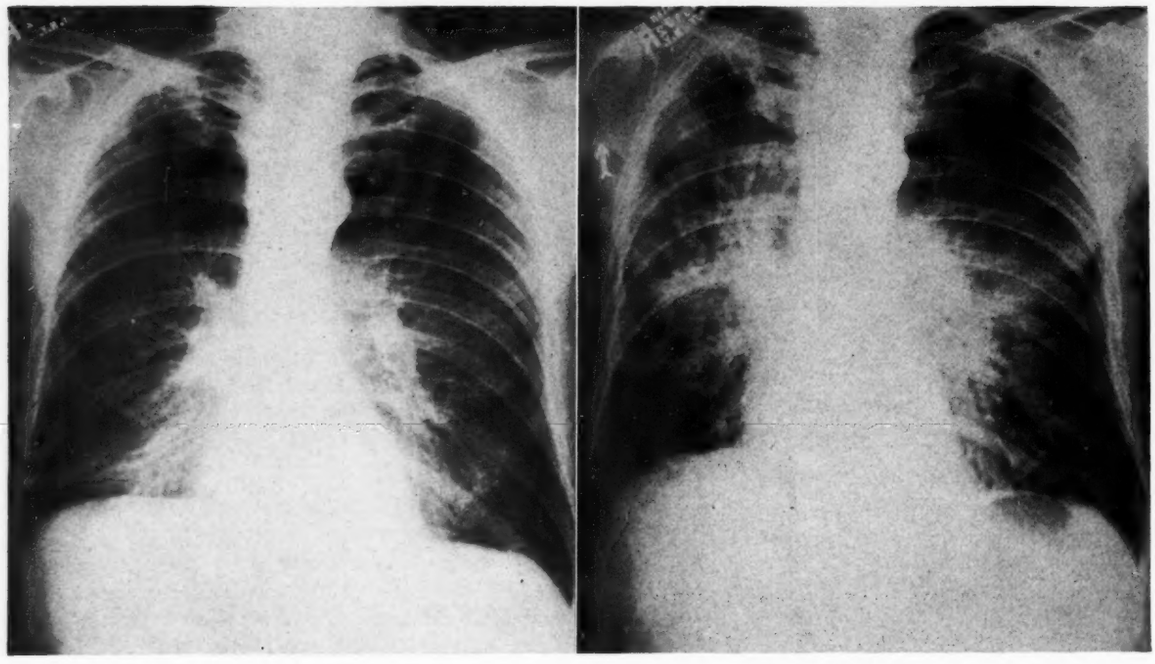

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FIG. 3. March 27, 1942, chest film taken in a PA projection with a target-film distance of 7 feet, showing increased density at the right base. This represents a partially atelectatic lobe, but there has been a marked improvement as compared with the previous films. The right hilar shadow is slightly less prominent. The left lung field is relatively clear.

FIG. 4. May 18, 1942, eight days before death. There is a marked increase in density in the upper portion of the right lung and in the region of the left hilum. Most of the extra density is probably due to irradiation pneumonitis rather than due to the tumor.

Blood examination in November and December, 1941 showed hemoglobin 74 to 80 per cent; erythrocytes 3,200,000; leukocytes 15,000; neutrophiles 70 per cent, lymphocytes 20 per cent, mononuclears 7 per cent and eosinophiles 2 per cent. Marked poikylocytosis and anisocytosis was present.

On January 12, 1942, at the Memorial Hospital, New York City, a bronchoscopic examination was made by Dr. Watson who found in the right main bronchus 3 cm. below the carina a heaped-up, granulating lesion obstructing the bronchus and having the appearance of a fungating carcinoma. Biopsy was taken and reported "epidermoid carcinoma, grade 3."

About one week after the last bronchoscopic examination the patient developed a severe cough with pain in the right chest. Fluoroscopic examination revealed pneumothorax with about one-half of the lung deflated. A large bulla of about 3 cm. diameter was visible in the upper lobe. The first series of x-ray treatments was given and after six weeks the extra density at the base of the right lung had partially cleared up. What density remained, Dr. Orville Henderson, roentgenologist, believed was due to irradiation pneumonitis rather than to tumor. Wheezing respiration was greatly relieved by ephedrine. There was gradual loss of weight during this time. A blood leukocyte count on March 20, 1942, was 8,800 and there was a mild hypochromic anemia.

In April, 1942, he was given a second series of deep x-ray exposures. The cough became much less but codeine ½ gr. four to six times daily was still necessary to alleviate pain. The right middle lobe at this time was about three-fourths inflated and the pulmonary shadow much reduced. (Fig. 3.) A summary of the x-ray treatments is as follows:

Deep x-ray therapy was instituted on January 26, 1942 by Dr. Orville Henderson, roentgenologist of the Samaritan Hospital, Troy, N. Y. The current was 22 kv. p., 20 ma., 80 cm. T.S.D., with filter of .5 mm. copper. Fields of the dimension of 15 by 15 cm. were used, one anterior, one posterior and two lateral directed at the right lung. Daily treatments were given with a total of 3,500 r anteriorly, 2,900 r

posteriorly and 2,000 r to each of the lateral fields.

Two weeks later, in April after the first series, severe pain in the right chest was accompanied by a pleural friction rub. There was an increase in the pulse rate to 120 with a temperature of 97.8°F. The right lung showed little expansion with fine râles anteriorly on both sides of the chest and impaired transmission of breath sounds posteriorly in the right lung. (Fig. 4.) On May 19th he was in great respiratory distress, requiring oxygen inhalation. His temperature was 100°F. but there was no increase in leukocytes. He died May 26, 1942.

The postmortem examination, as reported by Dr. Gustavus H. Klinck, Jr., at the Cluett Pathological Laboratory, Samaritan Hospital, Troy, N. Y., was as follows:

The body is that of an emaciated white man, 161 cm. in length. There is marked thoracic scoliosis to the right. As the body is turned much frothy, gray fluid flows from the mouth. The conjunctivae have a yellowish tint. The skin over the right thorax, anteriorly and posteriorly, is purplish brown, brawny, very adherent to the subcutaneous structures and in numerous places shows a delicate purple mottling.

The peritoneal cavity is free from fluid and adhesions. The diaphragm reaches to the level of the fifth intercostal space on the right and the sixth rib on the left. Pleural cavities are free from fluid. However, there is a thin film of sticky fibrin over the left lung causing adherence of most of the anterior and the greater part of the remaining surface of the lung to the pleura. A thick fibrous adhesion binds the extreme outer basal portion of the left lung to the diaphragm. The right lung is lightly attached to the chest wall posteriorly but the apex is firmly adherent. The pleura covering the anterior portion of this lung is thickened and has an opaque cobwebby appearance. The pleura over the posterior portion of the lower lobe, the middle lobe and the lower portion of the upper lobe is opaque, gray, wrinkled and measures about 1 mm. in thickness in its thickest portions. In the mediastinum there are a few very small but firm palpable nodes in the fat. Sections show small foci of glistening, grayish tissue. The pericardial cavity shows no significant change. The heart weighs 300 Gm. and appears enlarged, apparently due to dilatation of both ventricles, particularly the right. The epicardium and endocardium show no morbid change. The myocardium is flabby and

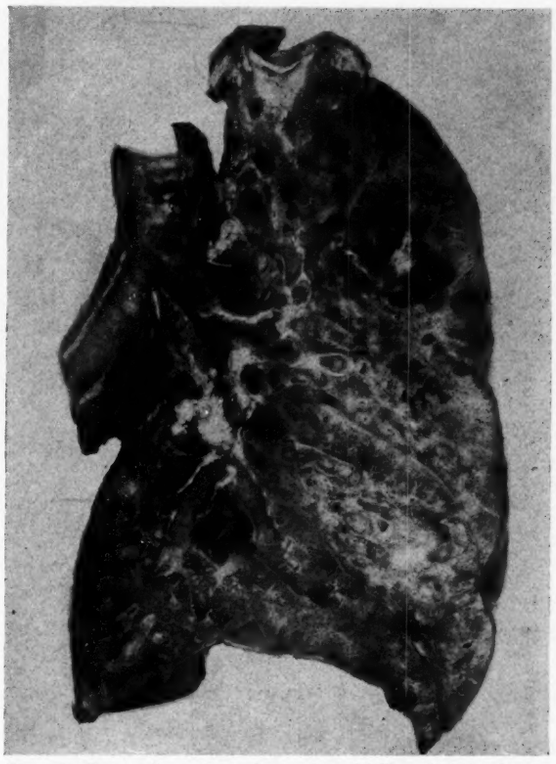

FIG. 5. Frontal section through middle of right lung. The white tumor mass is easily seen occluding the lower right bronchus just below its origin but extending upward as far as the carina tracheae. Peribronchial and perivascular extension has occurred. Elsewhere in the middle of the lower lobe there is much suppurative bronchitis with bronchiectasis. At the apex is a large collapsed bulla and in the peripheral zone of the right lobe bullous emphysema.

dark purple. The valve leaflets of both the tricuspid and mitral valves show small, nodular, rubbery thickenings along the edges. The chordae tendineae are shortened. The coronary arteries show a slight degree of thickening. The myocardium of the left ventricle measures 5 to 8 mm. The aorta shows a minimal degree of atherosclerosis.

Both lungs and trachea are removed and fixed by injecting formalin into the trachea according to the method of William Snow Miller and then suspending in Kaiserling I. Along the course of the right bronchus and at the bifurcation of the trachea are several reddish-gray and translucent, slightly firm lymph nodes, the largest of which is 3 by 1 by 1 cm. After fixation the lungs are re-examined.

The apex of the right lung has a very wrinkled appearance, apparently due to the presence of numerous cavities of collapsed bullae 1 to 2 cm. in diameter. The lung is further examined by

FIG. 6. An enlargement of the tumor-bearing area showing the occluding neoplasm with peribronchial extension and bronchiectasis.

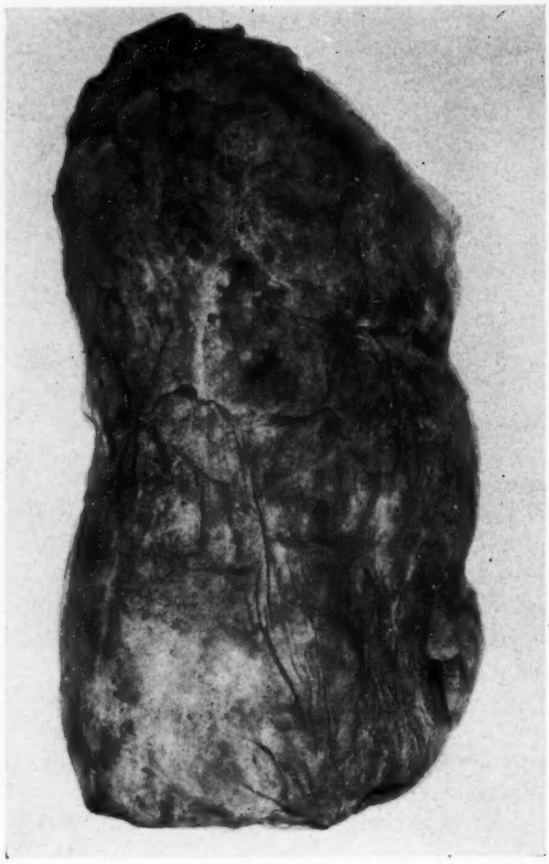

FIG. 7. Pleural surface of the right lung. Typical irradiation pleuritis, with pearly thickening and decrease in the normal wrinkling.

making a single frontal section through the mid-portion. The section passes through the main bronchus. The branch to the lower lobe is apparently occluded by a grayish-white mass of dense, rather crumbly tissue, irregular in outline, unencapsulated and invasive. It measures 3 by 4 cm. in cross section. The branches of the bronchial tree of the lower lobe beyond this lesion show marked dilatation and their linings are rough and gray and contain puriform material. Near the obstructive lesion in the bronchus is a cavity about 2 cm. in diameter with a rough, nodular gray lining. In general the tissues of the lower lobe are moderately firm and retain some crepitation. Some portions, particularly the middle lobe, appear very fibrous on palpation. The upper portion of the upper lobe shows marked emphysema with cavities up to 1 cm. in diameter. A cyst-like space, 3 cm. in diameter, occupies the extreme apex. The cyst wall averages 2 mm. in thickness and has a gray lining that can be stripped away in layers. (Figs. 5, 6 and 7.) In the left lung a bulla 3 mm. in diameter is found at the apex. Many other bullae 0.3 to 1.5 cm. in diameter are scattered in the subpleural zone of the median surface of the upper half of the lung but most of them are in the upper lobe. A paramedian incision discloses dense consolidation of the posterior half of the lower lobe becoming progressively less as the anterior portions of the lobe are approached. Thrombosis of several large blood vessels is found in the lower posterior portion. The upper lobe is soft and crepitant and shows all degrees of emphysema.

The spleen weighs 135 Gm. and is extremely soft. The capsule is smooth. Sections reveal purplish-brown tissue in which the usual markings are indistinct. The pancreas weighs 50 Gm. and is firm and pink. Parenchyma appears normal. The liver weighs 1,490 Gm. The capsule is smooth and thin. The consistence is about normal and the markings are distinct. The gallbladder contains one rough, round cholesterol stone 1.5 cm. in diameter and about 20 cc. of thick, black bile. The adrenal glands are slightly enlarged and show postmortem softening. In

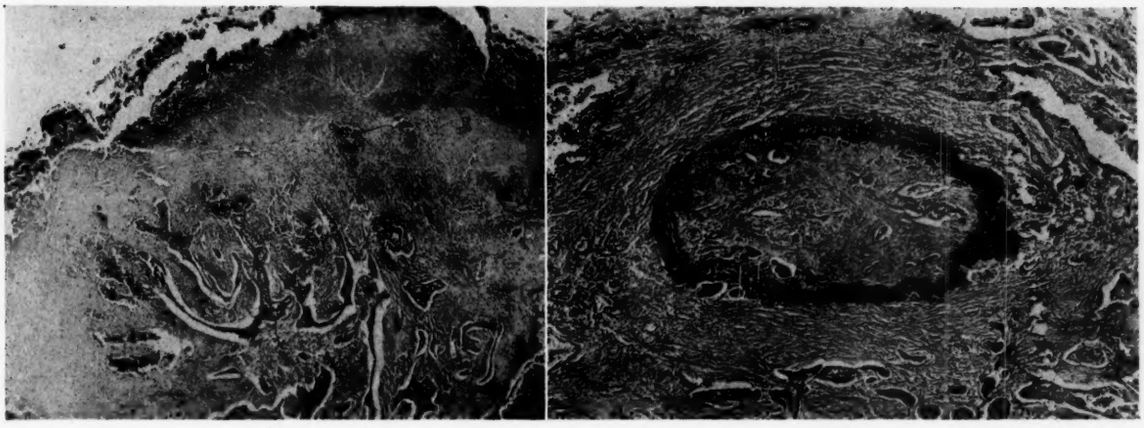

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FIG. 8. A portion of the primary tumor projecting into the bronchial lumen. The wide zone of hyaline necrosis is a typical irradiation effect as well as the degenerative changes in the outlying groups of tumor cells. In the central core squamous epithelial cords with some keratinizing areas are still visible.

FIG. 9. A photomicrograph of a vein adjacent to the main tumor showing invasion of a thrombus, apparently from an area in the lower left segment where the elastica has been disrupted (Verhoeff's elastic tissue stain).

general the cortex averages 1 mm. in thickness and is firm and yellow. The medulla is soft, red and mushy. In the cortex of the right adrenal is an adenoma 6 mm. in diameter. The left kidney weighs 190 Gm. Its capsule strips off easily, revealing a smooth congested surface. Section reveals edema but otherwise normal markings. The right kidney weighs 155 Gm. and resembles the left kidney. The wall of the bladder is edematous and the mucosa shows foci of congestion. A soft reddish-yellow plaque 1 cm. in diameter is attached to the floor posterior to the trigone. The bone marrow of the vertebrae is soft and dark red.

Anatomical Diagnoses: Squamous cell carcinoma of the right primary bronchus; bronchopneumonia of the lower lobe of the right lung with bronchiectasis; pleural adhesions with hyaline pleuritis of the right lung; pleural adhesions and acute pleuritis of the left lung; valvulitis, chronic rheumatic, of the mitral and tricuspid valves; bullous emphysema of both lungs; dilatation of the heart; hypertrophy of the myocardium of the right ventricle; dilatation of the thoracic duct; cholelith of the gallbladder; papilloma of the urinary bladder; congestion, passive, of the kidneys; x-ray reaction of the skin of the thorax.

Microscopically, the thymus is represented by a mass of fat tissue containing a few widely spaced, spheroidal, calcareous deposits. In the heart there is slight separation of the perivascular and intermuscular fibrous tissue by edema. The intima of the aorta shows atherosclerotic thickening and the media contains some calcareous deposits.

Sections from the main branch to the lower lobe of the lungs reveal numerous anastomosing and isolated cords and masses of anaplastic epithelial cells of squamous type with occasional foci of keratinization. The tumor cells are variously supported by dense, hyaline, almost avascular fibrous tissue, recently formed fibrous tissue and necrotic tissue. Almost all sections show a border of granular necrotic tissue containing masses of bacteria. There is also necrosis of the bronchial wall in this area. In some parts the lung tissue is sclerosed and alveoli are lined by cuboidal cells. The more intact lung shows slightly to moderately thickened alveolar walls. Most of the alveoli contain many lipoid phagocytes. At points 4 to 5 cm. from the site of the neoplasm there is much parenchymal sclerosis. Some alveoli contain organizing exudate. At the base of the right lung there is fibrinous exudate covering a hyaline fibrous layer beneath which is a zone of telangiectasis. Some small veins in the region of the tumor are occluded by organized thrombi in which there are many cords of tumor cells that have disrupted the elastica by direct invasion. The left lung contains much air-containing tissue but in the lower lobe the alveoli are filled with leukocytic exudate, fibrin and edema fluid. Lymph nodes from the hila contain no tumor. (Figs. 8, 9 and 10.)

There is much hemosiderin in the spleen. The lymphoid follicles are small and few. In the pancreas one large duct shows squamous metaplasia of the columnar epithelium. The liver and adrenal glands show parenchymatous

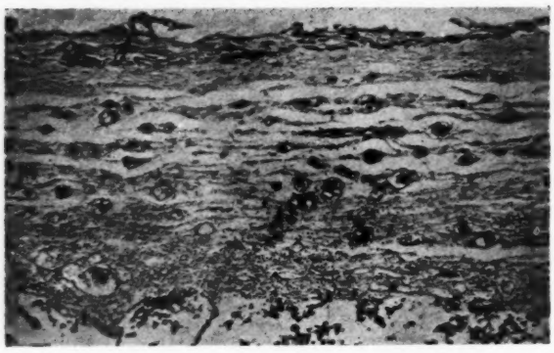


FIG. 10. Pleura of irradiated lung showing fibrin overlying hyalinized connective tissue. Beneath this layer are numerous dilated capillaries in a loose framework containing many lymphocytes.

degeneration. The kidneys are normal except for marked congestion. A papilloma is present in the mucosa of the bladder. The lymph nodes from the thoracic and abdominal groups contain no tumor. A postmortem blood culture reveals no growth obtained after ten days of incubation.

COMMENTS

This case then is one of squamous cell carcinoma of a right primary bronchus with complicating bronchitis, bronchiectasis, pneumonitis and emphysema. The neoplasm was relatively small but because of its strategic location gave clinical symptoms over a period of nearly three years. During this long interval it remained within an area roughly 2 by 3 cm., grew slowly in the peribronchial tissues and even invaded regional veins which built up a protective thrombosis, again holding the tumor within a narrow hilar zone. It had not even emerged in the hilar lymph nodes. It was found nowhere else in the body.

Four months before death deep roentgen ray therapy was instituted, repeated bronchoscopic examinations up to that time having failed to reveal the neoplasm. This treatment was followed by a diminution of the cough reflex and a decrease in shadow at the base of the right lung. However, in this short time, as autopsy proved, several typical tissue reactions occurred that can be attributed to the action of the rays: (1) a hyalinizing pleuritis; (2) a vascularization of telangiectatic type in the subpleural layer; (3) hyaline necrosis of the peripheral portions of the primary tumor.

The effects of the partial and finally complete obstruction of the bronchus by the tumor on the lung physiology were evident in the early dyspnea, cough, loss of strength, along with cyanosis and curving of the finger nails. These signs of anoxemia were far more pronounced than could be accounted for on the basis of lung tissue invaded by tumor, or pulmonary changes detectable by the usual methods of clinical examination, including x-ray studies. The entry of infecting organisms into the field supplied by the diseased bronchus provided an element practically always present in cases of bronchial carcinoma. The gradual development of bronchiectasis with focal bronchopneumonia deprived the patient of a large ventilating field as did the many emphysematous bullae.

Two series of deep x-ray treatments were given, totaling 10,400 r, divided among four portals. The postmortem evidence indicated a specific x-ray effect upon the pleura, subpleura, alveolar and vascular structures and very definitely upon the tumor itself. Hyaline necrosis of the peripheral zone of the tumor would seem to be a characteristic effect. The tumor was still viable in the central core but fragmentation of cells was occurring in the areas in which the dosage of rays was of sufficient depth. The tumor was of keratinizing type and hence somewhat radioresistant. The effect of the irradiation on the growth, then, was good as far as it went. The changes in the pleura and lung parenchyma were of course deleterious, and that poses the greatest problem in radiotherapy of tumors of the lung and elsewhere—how to destroy the tumor without seriously injuring the organ in which it grows.

Deep x-ray therapy of primary or secondary lung tumors is employed throughout the world where equipment and personnel are available. Radical lung surgery is successful in certain cases but too often one must be satisfied with such palliation as high voltage roentgen rays can offer.

But with all this clinical material, irradiation pulmonary or pleural fibrosis is not seen in every patient so treated. In 1925, Evans and Leucutia[5] in eighty cases found the incidence rare unless repetition of large doses was necessary. Eighty per cent however, showed fibrosis if the dose exceeded 140 per cent of the skin unit dose, and they decided the lung changes were dependent on the quantity of radiation rather than on its wave length.

Desjardins[6] in 1926 detected lung changes in only 2.5 per cent of several hundred cases in which the thorax received 800 to 1,000 r and never encountered it after 600 r. Age and arteriosclerosis were suggested as complicating factors. Lung vulnerability, according to Downs,[7] was increased by acute and chronic infections and arteriosclerosis. McIntosh[8] described four cases of pleuropulmonitis one to two months after irradiation of the thorax with accurate depth dose estimations, 2,000 to 4,000 r. Spencer and Warren[9] believed that pulmonary metastases had no significant relation to the development of irradiation changes.

Widmann[3] studied 273 cases of cancer of the breast in an effort to explain irradiation pulmonary fibrosis. He had used intensities of 1,600 to 2,000 r in one cycle, and 3,000 to 6,000 in two or more cycles (air) to each of three or four skin portals. In his series 22 per cent showed x-ray evidence of fibrosis and in 85 per cent of these there was metastatic lung cancer as proved at necropsy. Only 3.3 per cent of those alive three to ten years showed pulmonary fibrosis or, in other words, those clinically free from metastasis had the same incidence of irradiation changes as those with so-called normal lungs.

The mechanism of the dyspnea which invariably accompanies the pleura-lung fibrosis is not entirely clear, but Leach and his co-workers[1] believe there are at least four factors contributing: (1) a marked diminution of vital capacity because of the fibrosis itself; (2) fixity of the chest wall; (3) compensatory emphysema; (4) hyperirritable Hering-Breuer reflexes.

The most serious complications of a primary lung tumor are metastasis and bronchiectasis. This latter bronchial lesion may be due to partial obstruction of the bronchus by a papillary, polypoid or constrictive growth, or by a mass of granulation tissue or inspissated mucus superimposed along the mucosal tract. There are also effects of a reflex nature affecting the ventilating capacity of the lungs, but the intrabronchial suppuration and adjacent alveolitis contribute a massive focus of infection which is of major importance by adding to the mechanical respiratory problem a bacteriotoxic factor.

Intensive treatment of bronchiectasis is imperative in preserving life in patients with lung cancer. An excellent review of this subject up to 1941 is found in an article by Riggins[10] who discussed the various medical measures of the time. Since x-ray therapy for bronchiectasis had been urged by Berck,[11] this modality was scrutinized critically and found unsatisfactory. Lobectomy or pneumonectomy was advised by Riggins for suitable patients in the hands of experienced thoracic surgeons. In the case here reported there was no evidence of a favorable effect upon the bronchiectasis of the two courses of deep x-ray irradiation. In controlling the bacterial flora, penicillin, streptomycin, and the sulfonamides have found an important place in the modern treatment of chronic bronchial infections and should be employed early in the management of primary or secondary lung cancer.

SUMMARY

1. Cancer of the lung endangers life by reason of (1) its location with reference to large bronchial trunks; (2) the rapidity of growth of the primary lesion; (3) its metastatic spread; (4) the high incidence of pulmonary infection, usually with some degree of bronchiectasis.

2. A case is presented of a relatively small squamous cell carcinoma of the

lower right bronchus, arising near the hilum and causing marked bronchiectasis and pneumonitis. Deep x-ray therapy effectively prevented spread of the tumor from a narrow hilar zone but injured the pleura and lung parenchyma.

3. While some roentgenologists have employed deep x-ray technic in the treatment of bronchiectasis, there was no evidence of a favourable influence on this complication of the two courses of x-ray exposures totalling 10,400 r.

4. Since pulmonary infection is an almost constant finding in patients with lung cancer, intensive treatment with penicillin and/or sulfonamides or streptomycin should be the rule, whether or not radical surgery or deep x-ray therapy is employed. This might at least improve the patient's general condition and thus add to his life expectancy as well as make him a better operative risk.

5. There is need for further refinements in the control of high voltage roentgen therapy of cancer of the lung in order to prevent harmful reactions in normal pleura and lung parenchyma.

REFERENCES

1. Leach, J. E., Farrow, J. H., Foote, F. W., Jr. and Wawro, N. W. Fibrosis of the lung following roentgen irradiation for cancer of the breast. *Am. J. Roentgenol.*, 47: 740–747, 1942.
2. Leach, J. E. Abnormal pulmonary physiology as a result of chronic irradiation pleuropulmonitis. *Am. J. Roentgenol.*, 50: 772–778, 1943.
3. Widmann, B. P. Irradiation pulmonary fibrosis. *Am. J. Roentgenol.*, 47: 24, 1942.
4. Jacobsen, V. C. The deleterious effects of deep roentgen irradiation on lung structure and function. *Am. J. Roentgenol.*, 44: 235–248, 1940.
5. Evans, W. A. and Leucutia, T. Intrathoracic changes induced by heavy radiation. *Am. J. Roentgenol.*, 13: 203–220, 1925.
6. Desjardins, A. U. Reaction of the pleura and lungs to roentgen rays. *Am. J. Roentgenol.*, 16: 444–448, 1926.
7. Downs, E. E. Lung changes subsequent to irradiation in cancer of the breast. *Am. J. Roentgenol.*, 36: 61–64, 1936.
8. McIntosh, H. C. Changes in lungs and pleura following roentgen treatment of cancer of the breast by prolonged fractional method. *Radiology*, 23: 558–566, 1934.
9. Warren, S. L. and Spencer, J. Radiation reaction in the lung. *Am. J. Roentgenol.*, 43: 682–701, 1940.
10. Riggins, H. M. Bronchiectasis. *Am. J. Surg.*, 54: 50–67, 1941.

Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE EASTERN SECTIONAL MEETING HELD IN NEW YORK, DECEMBER 12, 1947

FAMILIAL IDIOPATHIC DYSPROTEINEMIA. I. CLINICAL DESCRIPTION OF A NEW SYNDROME. *F. Homburger, M.D., New York, New York.* (From the Sloan Kettering Institute for Cancer Research.)

A new syndrome, familial idiopathic dysproteinemia, was found in a mother, four of her adult children and two of her grandchildren. The syndrome is characterized by hypoproteinemia and/or changes in the electrophoretic plasma protein patterns, by peripheral vascular disturbances (low oscillometric indices in the females, ulcers of the legs in the males) and by anomalies of the thoracic cage.

In one case protein metabolism was studied and it was found that no regeneration of plasma protein occurred while the patient was in positive nitrogen balance. Plasma protein was readily mobilized to replace small amounts of protein acutely withdrawn by plasmapheresis. Injected albumin disappeared from the circulation at the same rate as in a normal control subject. The disappearance rate of injected γ-globulin, however, was rapid and antibody formation (isohemagglutinins and pneumococcus polysaccharide antibodies) was defective. These findings demonstrate the complexity of the homeostasis of plasma proteins and suggest the existence of hereditary factors governing these mechanisms.

STUDIES IN COPPER METABOLISM IN PATIENTS WITH MELANOMA. *J. B. Trunnell, M.D., A. H. Minor, M.D.* and *N. F. Young, Ph.D., New York, New York.* (From the Sloan Kettering Institute for Cancer Research.)

Because melanoma tissue has been shown to contain concentrations of copper second only to the liver, studies have been undertaken to assess the possibility of significant intracellular radiation therapy with radioactive copper. Cu^{61} and Cu^{64} have been employed in a patient with metastatic melanoma. Observed were: (1) Rapid disappearance of intravenously administered copper from the circulation, followed by reappearance after about two hours increasing up to twenty hours; (2) rapid appearance in the liver and bile; (3) low total urinary and fecal loss; (4) slow and scant concentration in melanoma tissue.

In a second patient efforts were made to create copper deficiency prior to administration of Cu^{64} so that pick-up by melanoma might be increased.

BAL was found to increase the urinary excretion of copper by a factor of three. Prolonged administration of BAL during a period of low copper intake (di-thio-carbamate used for copper determinations) was found not to mobilize copper from the body, probably because it appears to be metabolized.

RÔLE OF BILE IN THE ABSORPTION OF STEROIDS FROM THE GASTROINTESTINAL TRACT. *M. M. Hoffman, M.D., Montreal, Canada.* (From the McGill University Clinic, Royal Victoria Hospital.)

Since bile is required for the optimum absorption of cholesterol from the gastrointestinal tract, it has been assumed that bile is also essential for enteral absorption of steroid hormones and related substances. On this assumption, bile salts have been administered simultaneously with steroid hormones to patients and experimental animals in an endeavor to enhance the effectiveness of the latter substances. To determine if this assumption is correct effect of the absence of bile from the gastrointestinal tract on the absorption of steroid hormones was studied. Dehydroisoandrosterone, progesterone and desoxycorticosterone acetate were individually administered by gavage to normal rabbits and to rabbits in which the bile ducts had been ligated. In each

instance the amounts of metabolites excreted in the urine of the normal animals were compared with the amounts excreted by the animals with ligated bile ducts. It was found that following administration of dehydroisoandrosterone to animals in which bile was absent from the gastrointestinal tract, the amounts of 17-ketosteroids in the urine were equal to those excreted by the normal animals similarly treated. Pregnanediol glucuronide was excreted in the urine following administration of progesterone and desoxycorticosterone acetate to the animals with ligated bile ducts. It is therefore concluded that absorption from the gastrointestinal tract of dehydroisoandrosterone, progesterone and desoxycorticosterone acetate can take place in the absence of bile.

ADRENAL CORTEX RESPONSIVENESS TEST: EVALUATION OF RESULTS IN GASTRIC CANCER. *Edward C. Reifenstein, M.D., F. Homburger, M.D., N. F. Young, Ph.D.* and *Aurelia Potor, M.D., New York, New York.* (From the Department of Clinical Investigation of the Sloan-Kettering Institute, Memorial Hospital Cancer Center.)

Injection of anterior pituitary adrenocorticotrophic hormone induces a fall in the blood eosinophile level and a rise in the urinary uric acid/creatinine ratio in persons with normally responsive adrenal cortices. Because of evidence suggesting that patients with cancer may have disordered function of the adrenal cortex, this test has been applied to patients with gastric cancer. Preliminary results (fifteen patients) indicate that although adrenocorticotrophic hormone in the dosage used induces the expected fall in the eosinophile level, it produces no significant change in the uric acid/creatinine ratio in the majority of these patients. The most striking finding is the discrepancy between these two responses. It remains to be determined whether or not the adrenal cortical mechanism for regulating urinary uric acid/creatinine ratio in these patients is unresponsive to pituitary trophic hormone stimulation because it is less sensitive or because it is functioning at the limit of its capacity.

FACTORS INFLUENCING THE EOSINOPHILE CONTENT OF NASAL SECRETION. *Thomas H. Holmes, M.D.* and *Helen Goodell, B.S., New York, New York.* (From the New York Hospital and the Department of Medicine, Cornell University Medical College.)

Eosinophile counts of nasal secretions in a group of twenty-five subjects were made. Fresh, wet nasal mucus was mixed in a test tube with a small amount of Hastings' stain and was mechanically agitated for two minutes with a stirring rod. The occurrence of 1 per cent eosinophiles in the total count of cells was considered significant. An increase in the eosinophile content of nasal secretions accompanying hyperemia, engorgement, hypersecretion and obstruction in the nose occurred in response to the following threats: (1) Specific threats, i.e., chemical agents, infectious agents and pollens directed at the nasal mucous membrane. (2) A specific threat directed at parts of the head other than the nose, i.e., noxious stimulation by a tight band inducing head pain. (3) General threats to bodily function, i.e., life situations evoking resentment.

Presence of increased numbers of eosinophiles in the nasal secretions together with hyperemia, engorgement, hypersecretion and obstruction apparently constitute a part of the protective pattern of shutting out and washing away agents noxious to the nasal mucosae as well as other threats and assaults directed against the integrity of the individual.

METABOLIC STUDIES ON A CASE OF ACROMEGALY WITH SPONTANEOUS DISAPPEARANCE OF DIABETES MELLITUS. *T. P. Almy, M.D.* and *Ephraim Shorr, M.D., New York, New York.* (From the Russell Sage Institute of Pathology, the Department of Medicine, Cornell University Medical College, and the New York Hospital.)

A patient who had typical acromegaly for fourteen years and severe diabetes mellitus for five years became suddenly ill with otitis media, mastoiditis and basilar meningitis. During this illness glycosuria and hyperglycemia completely disappeared and have not reappeared during a five and one-half-year period of follow-up. There were associated changes in somatic growth disturbances, gonadal function and basal metabolism, suggesting that the patient had suffered damage to the anterior pituitary. Metabolic study conducted five years after disappearance of the diabetes indicates that the patient can now produce insulin and metabolize glucose in approximately normal amounts.

Appearance and disappearance of diabetes in this patient, apparently attributable to disturbances in the anterior pituitary, are considered in the light of our growing experimental knowledge of the rôle of the pituitary in carbohydrate metabolism.

NEW CONCEPT OF TRAUMATIC DIABETES. *A. J. Kauvar, M.D.* and *(by invitation) M. G. Goldner M.D. Ft. Logan, Colorado.* (From the University of Colorado School of Medicine and Veterans Hospital.)

Diabetes is now recognized as being traumatic in origin only when it develops following direct injury to the pancreas. Modern physiology has shown that the body reacts to trauma with a general metabolic response and it becomes more and more evident that the "alarm reaction" is of as great clinical importance as is the locally sustained traumatic injury. Carbohydrate metabolism has been found to be involved intimately in adaptation of the organism to the traumatic reaction.

The purpose of this presentation is to relate a series of clinical observations in which a diabetic syndrome developed abruptly in connection with sudden severe illness (coronary occlusion, pulmonary embolism, abdominal surgery, septicemia, fracture of femur). An attempt is made to interpret the pathogenesis in these cases on the basis of a functional disturbance of the metabolic response to an emergency situation, rather than as the result of primary organic disease of the pancreas.

In only two cases could diabetic heredity be established. In all instances the onset of the disease was severe, requiring vigorous insulin treatment. Ketosis was present in two cases. With improvement of the precipitating disease, the diabetes showed marked amelioration.

Since the modern concept of trauma comprises not only local reaction to injury but the bodily response as well, it is proposed to broaden the concept of traumatic diabetes to include recognition of the alarm reaction as an etiologic mechanism.

EXPERIMENTAL STUDY OF THE LIFE SITUATIONS, EMOTIONS AND THE OCCURRENCE OF ACIDOSIS IN A JUVENILE DIABETIC. *Lawrence E. Hinkle, Jr., M.D.* and *Stewart Wolfe, M.D., New York, New York.* (From the New York Hospital and the Departments of Medicine and Psychiatry, Cornell University Medical College.)

Clinical experience in the past has suggested that the course of diabetes mellitus can be influenced by life situations which induce certain emotional changes in the patient. Substantiation of this depends upon direct correlation of changes in the metabolic state with emotional states in diabetic subjects. The present report concerns such a detailed study in the case of a fifteen year old school girl who, despite careful regulation of insulin dosage and dietary intake, recurrently became acetonuric and required admission to the hospital twelve times within a period of five years.

She was found to be anxious, insecure and in constant conflict with her tyrannical mother. During one hundred days of observation it was found that she developed ketonuria on nine occasions, immediately after the onset of a situation which produced intense anger or fear. There were only nine such situations during the observation period and all were followed by ketonuria.

Further control of the experimental situation was achieved during a period of ten days when the patient was hospitalized and subjected to rigid control of dietary intake, insulin and muscular activity. Following a suitable control observation in the setting of a major threat to her personal security, she became intensely frightened and angry. Ketonuria appeared within twelve hours, was sustained throughout the period of stress and finally disappeared after the reassurance and reestablishment of security.

Thus alteration in the carbohydrate and fat metabolism as manifest by development of ketonuria appeared to be directly related to the emotional state and security of the subject.

SICKLING IN NEGRO NEWBORNS: ITS POSSIBLE RELATIONSHIP TO FETAL HEMOGLOBIN. *Janet Watson, M.D., Brooklyn, New York.*

Sickling preparations were made in 226 consecutive newborn negro infants and their 226 mothers. The standard sealed slide preparation incubated at 37°C. was used. Of the 226 infants, nineteen or 8.4 per cent showed sicklemia; of the 226 mothers, eighteen or 8.0 per cent showed sicklemia. Although the incidence of sicklemia was almost identical in the two series, two differences in regard to the sickling became

evident: First, a time interval of forty-eight hours was often required for maximum sickling of the infants' red cells in contrast to the twenty-four-hour period necessary for the mothers' cells. Secondly, the infants' red cells showed only 0.5 to 29.5 per cent sickling while the mothers' cells showed 84 to 100 per cent sickling.

Fetal hemoglobin differs chemically from adult hemoglobin in several respects and, as tested by the alkali denaturation method, does not disappear from infants' blood until the age of four and one-half months. It is interesting that one of our patients with sicklemia followed from birth developed progressively increased sickling from 6 per cent at birth to 90 per cent at four and one-half months. This is also correlated with the estimated four-month life span of the erythrocyte. In view of these data it is suggested that the low percentage of sickling in newborns is due to the presence of fetal hemoglobin, and that this fetal hemoglobin accounts for the absence of death from sickle cell disease *in utero* where the low oxygen tension would otherwise cause sickling with the usual disastrous pathologic sequelae.

SENSITIVITY OF THE TUBERCLE BACILLUS TO STREPTOMYCIN BEFORE AND DURING THERAPY OF PULMONARY TUBERCULOSIS. *Joseph F. Sadusk, Jr., M.D.* and (*by invitation*) *William E. Swift, Jr., M.D., New Haven, Connecticut.* (From the Department of Internal Medicine, Yale University School of Medicine.)

In vitro sensitivity of tubercle bacilli isolated from sputa or gastric contents was determined in a group of sixteen patients with pulmonary tuberculosis receiving 1.8 Gm. of streptomycin daily for a period of four months. *In vitro* tests were performed in Dubos medium.

In all sixteen cases the strains of bacilli isolated prior to treatment were highly sensitive to streptomycin. Fourteen of these sixteen strains were inhibited by 0.5 microgram of streptomycin per ml., the remaining two strains were inhibited by 1.0 microgram per ml. Loss of sensitivity (ten-fold increase in resistance) began to appear by the end of the first month of therapy together with conversion of positive sputum or gastric washings to negative in other cases as determined by culture. By the end of the third and fourth months of therapy cultures were positive in only nine of the sixteen patients. Tests of organisms from these nine positive cultures indicated that all of them had developed a ten-fold or greater increase in resistance. Five of these nine strains developed a ten to fifty-fold increase in resistance; the remaining four strains developed a 100 to greater than 2,000-fold increase in resistance.

It was not possible with this small group of patients to demonstrate conclusively a correlation between resistance to streptomycin and the clinical course under therapy.

TREATMENT OF PNEUMOCOCCIC MENINGITIS BY SYSTEMIC PENICILLIN. *H. F. Dowling, M.D., L. K. Sweet, M.D.* and *H. L. Hirsh, M.D., Washington, D. C.*

When penicillin is employed in addition to sulfonamides, the fatality rate in pneumococcic meningitis is reduced below that obtained with sulfonamides alone. Nevertheless, results obtained up to the present are far from satisfactory. According to accepted methods of treatment, penicillin is given intrathecally in amounts of 10,000 to 20,000 units per day and systemically in doses of about 500,000 units a day with full doses of sulfadiazine or sulfamerazine systemically.

Intrathecal administration of penicillin possesses many disadvantages. Among these are: (1) The possibility of radiculitis or convulsions developing when large amounts are given or when concentration of penicillin in the cerebrospinal fluid reaches high levels; (2) irritative action of penicillin upon the meninges, evidenced by development of pleocytosis and the possibility that this may cause adhesions and block; (3) difficulty and danger of repeated lumbar punctures. Intrathecal penicillin is employed because many investigators have failed to find demonstrable amounts of penicillin in the cerebrospinal fluid after systemic administration. Others have shown, however, that when sufficiently large doses of penicillin are given systemically, therapeutic levels are consistently obtained in the cerebrospinal fluid.

After preliminary studies had demonstrated that a therapeutic concentration of penicillin was consistently present in the cerebrospinal fluid of subjects receiving 1,000,000 units of penicillin intramuscularly every two hours we administered this dose plus sulfadiazine and sulfamerazine to patients with pneumococcic meningitis. Two patients received one intrathecal dose of penicillin; six received none. Five

patients recovered and three (37.5 per cent) died. In all fatal cases death occurred within twelve hours of the first dose of penicillin. All the patients who died were in unfavorable age groups and had been ill for some time before admission to the hospital. Among fifty-three patients treated by us with smaller amounts of systemic, plus daily intrathecal penicillin, 60 per cent died, and fever and pleocytosis were more prolonged than in those patients given no intrathecal penicillin or only given a single dose. Clinical and laboratory observations on the patients in the two groups are compared.

ENZYME INHIBITION BY ALPHA-TOCOPHEROL PHOSPHATE: EFFECT ON CERTAIN RESPIRATORY AND PROTEOLYTIC SYSTEMS AND ON BLOOD COAGULATION. *K. L. Zierler, M.D.* and *(by invitation) D. Grob, M.D.* and *J. L. Lilienthal, Jr., M.D., Baltimore, Maryland.* (From the Physiological Division, Department of Medicine, Johns Hopkins University and Hospital.)

Alpha-tocopherol phosphate (α-TPh) slows the accelerated oxidative processes in muscle dystrophy associated with vitamin E deficiency. α-TPh, *in vitro*, inhibits the succinoxidase system. In an effort to elucidate the mechanism of inhibition, studies were undertaken concerning the effect of α-TPh upon a number of enzyme systems. The systems were selected because they shared with the succinoxidase system a requirement for ionic calcium or because they contained sulfhydryl enzymes. (1) The adenosinetriphosphatase system was not influenced by α-TPh when optimal calcium concentration was maintained. (2) Coagulation of recalcified human plasma was prevented by α-TPh even when the molar ratio of ionic calcium to α-TPh was 10:1. Furthermore, as little as 10^{-8} M of α-TPh inhibited clotting of a thrombin-fibrinogen system. (3) α-TPh slightly inhibited the sulfhydryl enzyme papain. α-TPh inhibited trypsin, plasma protease and leukoprotease as effectively as did the specific antiproteases.

When α-tocopherol phosphate was injected into normal rats, large doses uniformly produced apparent drowsiness, ataxia and weakness; occasionally, convulsions and death. When the animals were sacrificed during the period of "drowsiness," succinoxidase activity of muscle and of brain was normal. Oxygen consumption of the diaphragm in Ringer-phosphate solution, however, was reduced while that of the brain was normal.

α-TPh, therefore, is anti-oxidative, anticoagulant and antiproteolytic.

DYSTROPHICA MYOTONIA. *C. S. Nadler, M.D., Manrico Troncelleti, M.D.* and *(by invitation) William Steiger, M.D.* and *Thomas M. Durant, M.D., Philadelphia, Pennsylvania.*

The present studies confirm Waring's concept of dystrophica myotonia, i.e., it is a heredogenerative disease, predominated by a modified Mendelian dominant gene. This is further modified by a type of mutation which is exhibited by progressive inheritance.

Dystrophica myotonia patients present the endocrine features of a specific type of hypogonadism. This is described by and called "Klinefelter's syndrome" which is characterized by small testes, aspermatogenesis, increased excretion of follicle-stimulating hormones and decreased excretion of 17-ketosteroids. Our patients also were compatible with Heller and Nelson's modification of this syndrome, i.e., "Leydig cell failure." Autopsy of one male patient with dystrophica myotonia showed, in addition to hyalinization of the seminiferous tubules, a decrease in the size of the adrenal and thyroid gland. Participation of the latter glands in the etiology of dystrophica myotonia and Klinefelter's syndrome is discussed. The beneficial effect of large doses of testosterone propionate in males is described.

Thus clinical and laboratory evidence seems to indicate that the etiology of dystrophica myotonia is that of defective genes which, through an evolution of status degenerans, cause secondary changes. These changes characteristically affect the lens of the eye, the muscular, vascular and endocrine systems.

EFFECT OF CHRONIC POISONING WITH DI-ISOPROPYL FLUOROPHOSPHATE ON NEUROMUSCULAR FUNCTION IN THE CAT. *Carlton C. Hunt, M.D.* and *Walter F. Riker, M.D., New York, New York.* (From the Department of Pharmacology, Cornell University Medical College.)

Di-isopropyl fluorophosphate (DFP) has been shown to inactivate irreversibly serum and tissue cholinesterase. Following large doses of DFP,

cats developed a protracted syndrome of muscular weakness lasting as long as five months. In the present study effects of repeated large doses of DFP in the cat were studied by symptomatology, neuromuscular function and cholinesterase activity of nervous and muscle tissue.

Cats which had received from two to six (average of four) daily intramuscular injections of 1 mg./kg. of DFP in oil showed ataxia, extreme muscular weakness and generalized fasciculations. Following the disappearance of fasciculations on the third to fourth day after poisoning, the animals showed generalized weakness and fatiguability. Subsequent to this recurrence of the weakness developed which was chiefly confined to the hind limbs and which lasted from 21 to 147 days.

At varying intervals after poisoning the response of the muscle to intra-arterial injection of acetylcholine and the response to nerve stimulation was studied. Increased sensitivity to acetylcholine was present (one to ten days) and a prolongation of the contractile response (four to eighteen days) resembling that seen after denervation. The muscle was unable to maintain a tetanus induced by indirect stimulation (one to six days). Regeneration of muscle cholinesterase activity was complete in two weeks. By one month the brain cholinesterase had reached 69 per cent and the nerve 85 per cent of their control values.

It is concluded that the syndrome described results from extreme reduction of muscle and nervous tissue cholinesterase by DFP. Changes in the response of the muscle to acetylcholine following protracted inactivation of cholinesterase suggest the development of an injury at the myoneural junction resembling that associated with denervation.

Observations on Spread of Pain.

E. Charles Kunkle, M.D., George C. Armistead, M.D. and *Helen Goodell, B.S., New York, New York.* (From the New York Hospital and the Department of Medicine, Cornell University Medical College.)

The digits of the hand as distinct projections of the body are particularly suitable for the study of spread of pain from a site of noxious stimulation. An effective and reproducible stimulus has been found in the immersion of a finger in water maintained at 0°c. Pain thus induced follows a conveniently cyclic course.

In one hundred experiments upon twenty-two adult subjects "cold" pain was nearly always found to overflow to adjacent areas, notably to neighboring digits. Features common to this phenomenon in almost all of the experiments were a "latent" period, "facilitation" in subsequent phases of the pain cycle, "tapering" of intensity and "incomplete segmental filling." The direction of spread was predominantly caudad in most instances. In no subject was contralateral extension of pain noted. Pain failed to spread from thumb to jaw (in cortical sequence). Overflow of pain was unaltered by preliminary interruption of the circulation to the arm or by procainization of an area into which spread of pain was to occur.

In contrast to these typical features of spreading pain, other and less "orderly" characteristics were noted. Most prominent was the moderate intraindividual and marked interindividual variation in extent of spread. In a minority of instances the spreading pain "migrated" during the experiment, "skipped" a digit or reached a higher intensity than that of the primary pain ("insubordination").

Many of these listed features of spreading pain have also been observed in patients with traumatic digital lesions, dental disease or angina pectoris. It is inferred that such overflow of pain is a central phenomenon and probably occurs at the segmental level in the cord. This mechanism contrasts sharply with spread of pain due to a peripheral effect, as in secondary contraction of skeletal muscle, and with reference of pain throughout the domain of a sensory nerve trunk as the result of a proximal nerve or dorsal root lesion.

Experimental Studies on the Nature of Hyperalgesia.

H. G. Wolff, M.D., J. D. Hardy, M.D. and *H. Goodell, B.S., New York, New York.* (From the New York Hospital and the Departments of Physiology, Medicine and Psychiatry, Cornell University Medical College.)

There are a number of varieties of hyperalgesia. Considered here is that which can be experimentally induced in areas of skin adjacent to sites of noxious stimulation as described by Sir Thomas Lewis. In these areas pain threshold is not lowered although pin pricks and thermal

stimuli above the pain threshold elicit more intense and longer lasting painful sensations than in control areas. Hyperalgesia develops from tissue injury in a procainized skin area as soon as the procaine effect begins to diminish. After hyperalgesia has become established complete procainization of the site of injury immediately eliminates hyperalgesia. Also the rate of development and spread, as well as elimination of the hyperalgesia by injection of procaine, are unaffected by occlusion of blood supply. Hyperalgesia develops in areas adjacent to prolonged thermal radiation inducing no more than threshold to minimal pain, and hyperalgesia does not persist longer than the stimulation. Pin pricks in the zone of hyperalgesia cause the minimal pain from the site of noxious stimulation to be intensified. These observations make it difficult to explain this type of hyperalgesia either on the basis of local liberation of a humoral substance in the site of hyperalgesia or a special nocifensor system as postulated by Lewis. On the basis of the aforementioned evidence it is suggested that hyperalgesia in areas adjacent to a site of noxious stimulation of the skin is dependent upon spread of a central excitatory state which results from a sustained barrage of noxious impulses from the periphery.

INTRA-OCULAR PRESSURE VARIATIONS IN GLAUCOMA ASSOCIATED WITH EMOTIONAL CHANGES. *Herbert S. Ripley, M.D., New York, New York.* (From the New York Hospital and the Departments of Medicine, Psychiatry and Surgery (Ophthalmology), Cornell University Medical College.)

In view of the long held opinion that personality factors play a part in the etiology or precipitation of attacks of glaucoma a study was undertaken in order to determine whether or not there was a relationship between emotional reactions and the level of intra-ocular pressure. Data concerning life history, eye symptoms and intra-ocular pressure were gathered on twelve patients with primary glaucoma. During interviews intra-ocular pressure and blood pressure were recorded.

Personality studies revealed a high incidence of the following characteristics: resentment, anxiety, moodiness, inordinate body preoccupation, conscientiousness, meticulousness, difficulty in maintaining satisfactory interpersonal relationships and sexual maladjustment.

Positive correlations were noted between development of a variety of difficult life situations and the presence of eye symptoms. During interviews, both with and without intravenously administered sodium amytal, fluctuations in intra-ocular pressure were found to be associated with psychodynamic factors and emotional variations. Conscious and unconscious psychic reactions, which appeared to disturb the balance between the sympathetic and parasympathetic nervous systems, resulted in both widespread vasomotor responses involving the systemic blood pressure and in localized reactions in the eyes. Elevations of intra-ocular pressure were associated with such varied emotions as anger, anxiety and depression. During periods of emotional calm, satisfaction or happiness lower intra-ocular pressures were obtained.

In one patient treated with personality analysis, explanation and reassurance there was simultaneous improvement in intra-ocular pressure and anxiety. This suggests that psychotherapy may have value in management of patients with primary glaucoma.

STUDIES IN EPILEPSY. *Wayne Barker, M.D.* and *Stewart Wolf, M.D., New York, New York.*

The relationship between convulsive symptoms and aggressive urges has been frequently discussed but the exact nature of the relationship has not been clarified. Sodium amytal interviews have been used to clarify the relationship between life problems and symptoms in other disorders. The relevance of certain situations and conflicts to the patient's disordered bodily function has been observed by means of changes in the intensity of symptoms which occur with changes in the content of such interviews.

This study was undertaken to ascertain, in similar fashion, the relationship between the pertinent problems and symptoms of an epileptic patient. The technic of electro-encephalography during sodium amytal interviews was used.

The patient's life history was characterized by a severe conflict between intense aggressive urges and strong needs for love and affection. Major convulsions and psychomotor seizures frequently occurred in situations in which aggressive wishes were aroused but were blocked by the situational circumstances. Clinical study and EEG confirmed the diagnosis of "epilepsy."

Under light sodium amytal narcosis (Gm. 0.3) the patient reacted an episode in which love and hate for his mother were in sharp conflict. An increasingly violent and intense state of rage culminated in an attack of grand mal clinically, and electro-encephalographically characteristic. The fit appeared to resolve, in a dynamic sense, the conflict between uncontrollable rage and the restrictions of conscience and society. The rôle of sodium amytal in the genesis of the reaction is discussed in terms of inactivation of cortical inhibitory influences.

ACTION OF NEOSTIGMIN IN SUPRAVENTRICULAR TACHYCARDIAS. *Samuel Waldman, M.D.* and *Louis Pelner, M.D., Brooklyn, New York.*

Supraventricular tachycardias of sinus, auricular and nodal origin can be successfully treated by the administration of 1 mg. of neostigmin methylsulfate intramuscularly. Action of this drug is predicated in these instances by its stimulating effect on the vagus nerve. Stimulation of the right vagus is the predominant factor in sinus tachycardia since this nerve ends especially at the sino-auricular node in which the disturbance originates, correction of which restores normal sinus rhythm. That this occurs is borne out by electrocardiographic studies on patients in whom the effect noted is a slowing of the heart by a decrease in rate of impulse formation at the sinoauricular node. An increased T-P interval is produced.

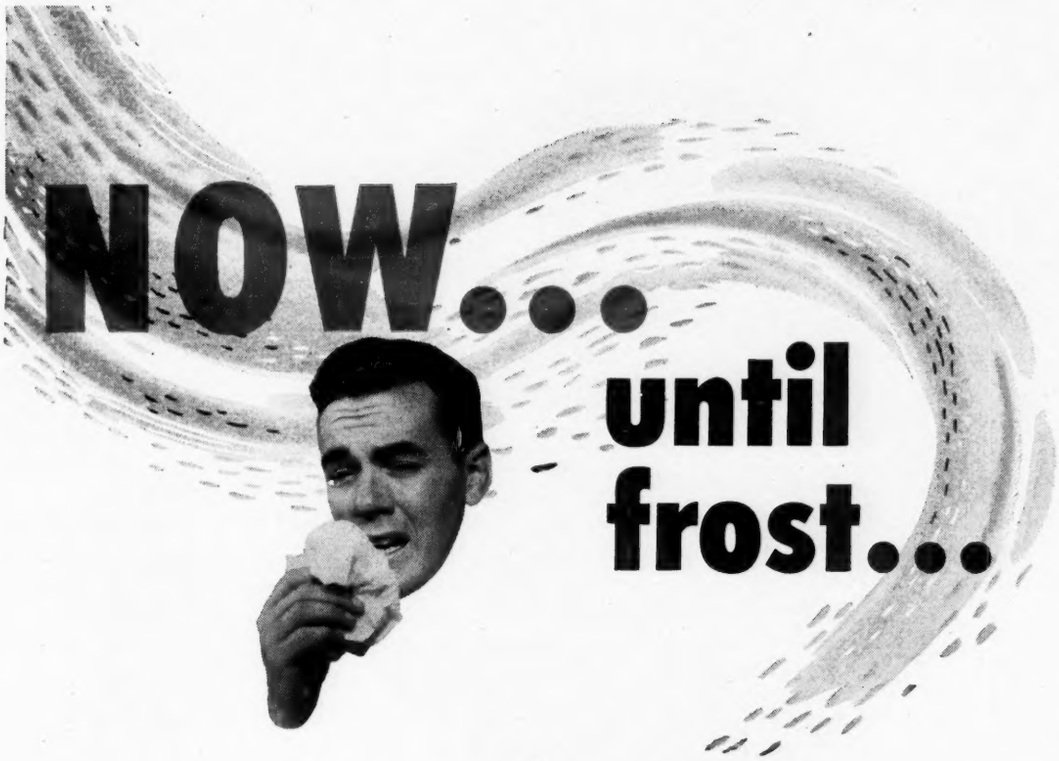
In the case of paroxysmal auricular and nodal tachycardias, stimulation of the right vagus would not correct this defect since the defect is not at the sino-auricular node. We could expect left vagal action to be effective since those fibers terminate mainly at the auriculoventricular node. Stimulation here would produce inhibition of conductivity and then induce a heart block of varying degree depending upon the extent of diminished conductivity. That this actually occurs is shown by electrocardiographic studies in those patients in whom heart block occurs varying from first degree block with increased P-R intervals to 2:1, 3:1 and 4:1 incomplete block. No case of complete block was found. After the block normal sinus rhythm was restored.

DIAGNOSTIC AND THERAPEUTIC USE OF TETRAETHYLAMMONIUM AND DIBENAMINE. *A. Dale Console, M.D., New York, New York.* (From the Department of Surgery, New York Hospital, Cornell Medical College.)

The effects of tetraethylammonium and dibenamine have been investigated in ninety-six patients with perivascular disease and hypertension. The beneficial effects of these drugs are dependent entirely upon the temporary vasomotor paralysis which they produce, and unless we assume that they have some additional beneficial action (which, as yet, has not been demonstrated) they can be only as effective as any other measure which produces a similar degree of vasomotor paralysis.

The physiologic state produced by sympathectomy differs markedly from that produced by temporary vasomotor paralysis regardless of how the paralysis is achieved. Temporary vasomotor paralysis, therefore, does not uniformly predict the results of sympathectomy in treatment save in some acute occlusions. Since the blockade produced by tetraethylammonium varies in extent and degree, it has been found even less reliable than paravertebral sympathetic block in predicting the results of sympathectomy in perivascular disease. Dibenamine, because it produces a block which may last from twelve to ninety-six hours, may be superior to other diagnostic tests in selecting patients with obliterative disorders for sympathectomy. Neither drug in our experience has proved to be of value in selection of hypertensive patients for sympathectomy.

In the treatment of acute vascular occlusions, temporary vasomotor paralysis may be of great value. Tetraethylammonium and dibenamine are both useful, but we prefer dibenamine because of the longer duration of action. In the chronic perivascular disorders the value of temporary vasomotor paralysis must yet be proved. Tetraethylammonium and dibenamine have not proved to be of greater value than other similar methods of treatment. It is doubtful that either drug is appropriate in the treatment of hypertension.



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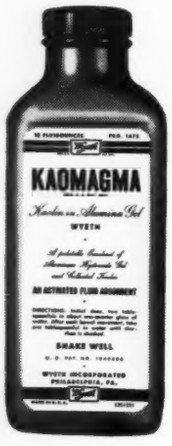

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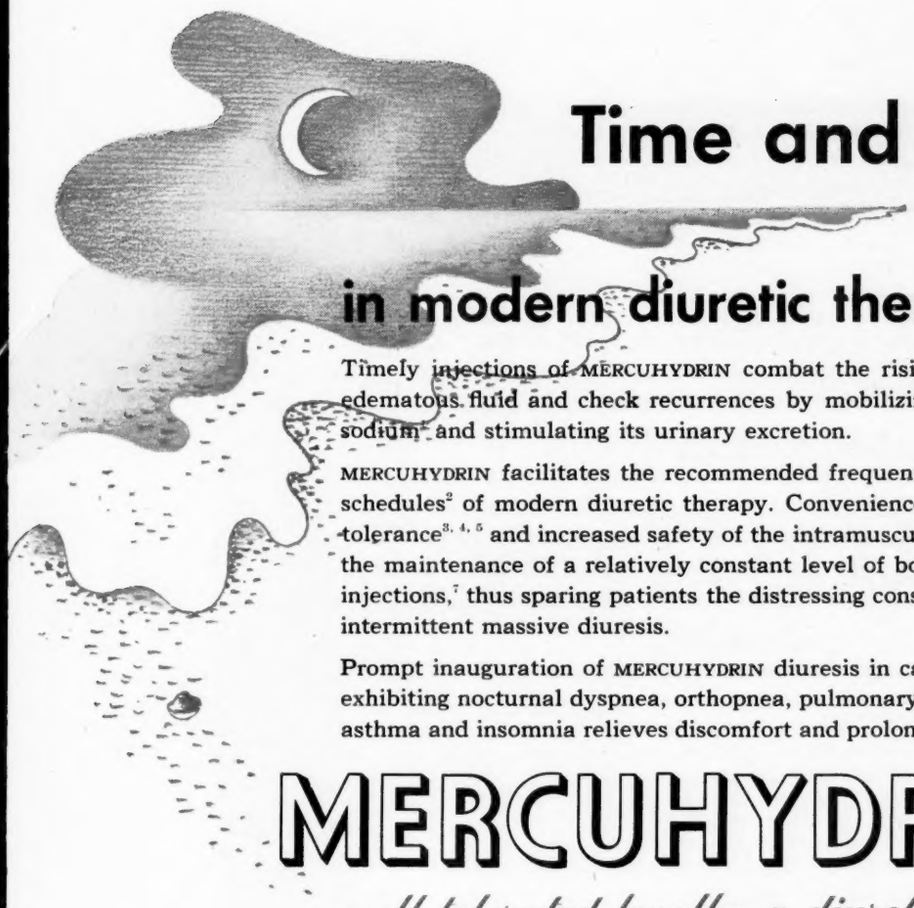

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1. Duca, C. J., and Scudi, J. V.: Proc. Soc. Exper. Biol. & Med. 66: 123 (1947).
2. Scudi, J. V., and Duca, C. J.: J. Urol. (to be published).

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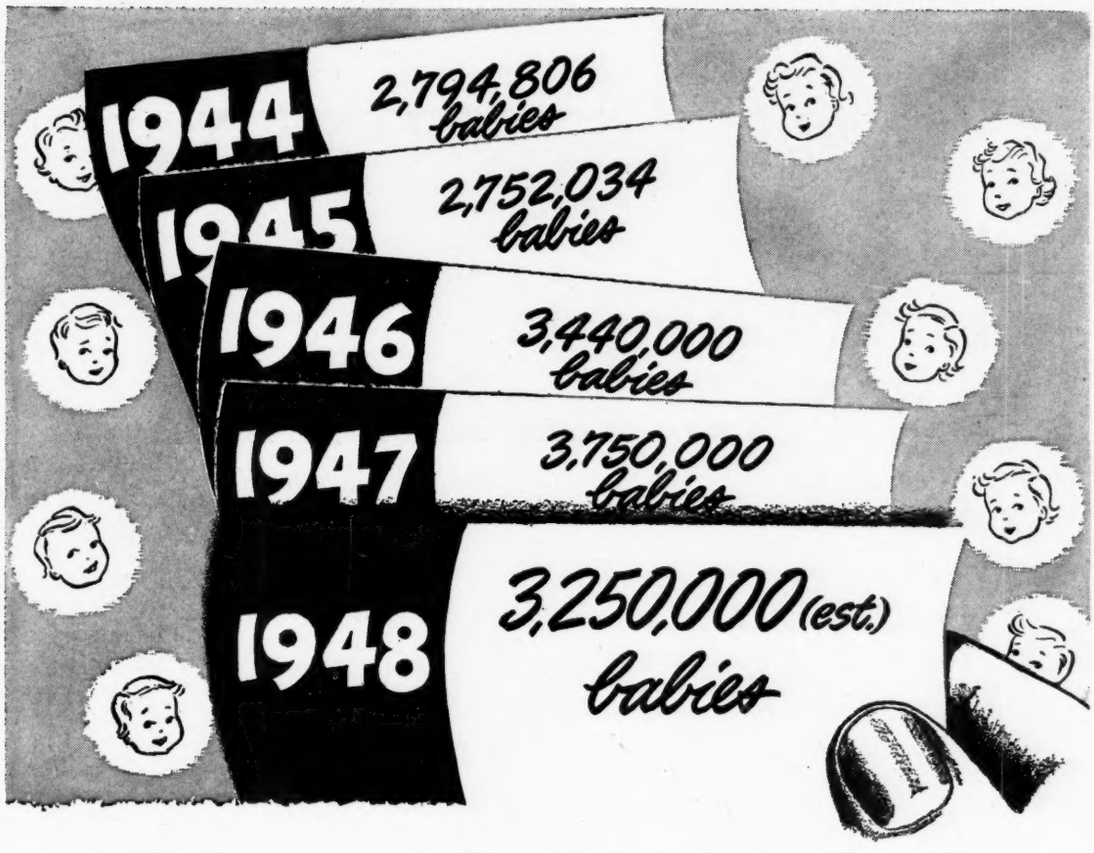

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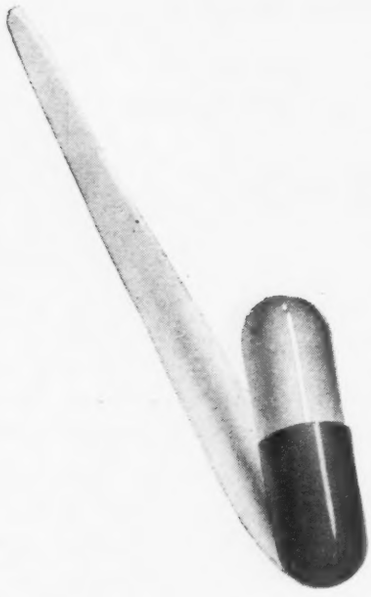

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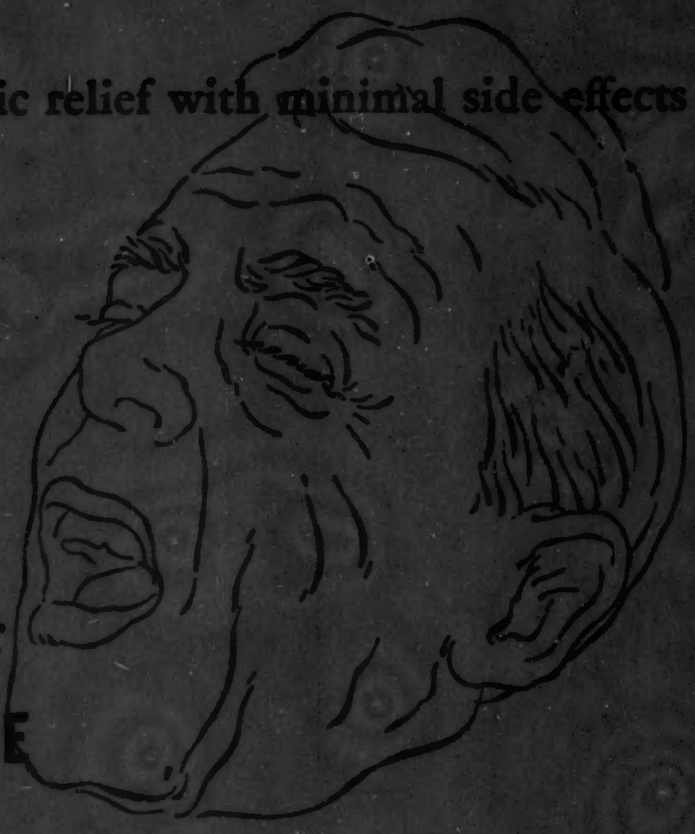

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1. Abbesman, C. E.: N. Y. *State Jl. of Med.*, 47: 1775, 1947.
2. Loveless, M. H.: *Am. Jl. of Med.*, 3: 296, 1947.
3. Bernstein, Rose and Feinberg: *Ill. Med. Jl.*, 92: 2, 1947.
4. Osborne, Jourdon and Rausch: *Arch. of Derm. & Syph.*, 55: 318, 1947.

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